

Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review

Structured Abstract

Objectives. To update a prior Systematic Review on the effects of omega-3 fatty acids (n-3 FA) on maternal and child health and to assess the evidence for their effects on, and associations with, additional outcomes.

Data Sources. MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and CAB Abstracts from 2000 to October 2014 (to be updated), eligible studies from the original report, and relevant systematic reviews.

Review Methods. We included randomized controlled trials (RCTs) of any defined dose of n-3 FA (or combination) compared to placebo, any other n-3 FA, or alternative dose, with an outcome of interest, conducted in pregnant or breastfeeding women or neonates (preterm or term). We also included prospective observational studies that analyzed the association between baseline n-3 FA intake or biomarker level and followup outcomes. Postnatal interventions began within a week of birth for term infants and within a week of beginning enteral or oral feeding for preterm infants. Standard methods were used for data abstraction and analysis, according to the AHRQ Methods Guide.

Results. We identified 3,893 potentially relevant titles from our searches, of which 74 RCTs (reported in 75 publications) and 43 observational studies met the inclusion criteria. Risk of bias was a concern with both RCTs and observational studies.

Maternal Exposures and Outcomes

Gestational length and risk for preterm birth: Strength of evidence (SoE) is low for a small positive effect of algal docosahexaenoic acid (DHA) or DHA-enriched fish oil—and for no effect of maternal supplementation with EPA+DHA-containing fish oil—on length of gestation compared with placebo; strength of evidence is low regarding an apparent lack of effect of DHA or DHA-enriched fish oil on risk for preterm birth..

Birth weight and risk for low birth weight: SoE is also moderate for a positive effect of prenatal algal DHA or DHA-enriched fish oil but not EPA or ALA on birth weight among healthy term infants ; maternal n-3 FA biomarkers were significantly associated with birth weight. Low SoE supports a lack of effect of maternal supplementation with DHA on risk for low birth weight..

Risk for peripartum depression: A low SoE supports a lack of effect of DHA, EPA, or DHA-enriched fish oil on (or association of n-3 FA with) risk for peripartum depression. .

Risk for gestational hypertension/preeclampsia: A moderate SoE supports a lack of effect of DHA supplementation on the risk for gestational hypertension or preeclampsia among high-risk pregnant women. Fetal, Infant and Child Exposures and Outcomes

Postnatal Growth Patterns: A moderate SoE supports a lack of effect of prenatal maternal supplementation with fish oil or DHA plus EPA on postnatal growth patterns (attainment of weight, length, and head circumference); a low SoE supports a lack of effect of pre- and postpartum maternal supplementation on these outcomes. A low SoE supports a lack of effect of DHA plus arachidonic acid (AA, an n-6 FA)-fortified infant formulas on growth patterns of

preterm or term infants. Visual Acuity: A low SoE supports a positive effect of prenatal DHA+AA on development of visual acuity in preterm and term infants, measured at 12 months of age.

Neurological Development: A low SoE supports a lack of consistent effects of prenatal DHA on any measure of neurological development.

Cognitive Development: A lack of consistent effect of prenatal maternal DHA supplementation was seen on a number of measures of cognitive development, such as the Bayley's Scale for Mental Development and IQ across many studies. A moderate SoE supports a lack of association of other prenatal n-3 FA interventions with any cognitive outcomes, adjusted for a number of factors. Low SoE supports a lack of effect of supplementing breastfeeding women with DHA plus EPA on cognitive outcomes; the SoE for other postnatal interventions such as n-3 FA-fortified infant formula is insufficient to draw conclusions.

Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and Learning Disorders (LD): SoE is insufficient to draw conclusions regarding an association of n-3 FA status with risk for ASD. No studies were identified on n-3 FA and risk for ADHD or LD.

Atopic Dermatitis (AD), Allergies, and Respiratory Disorders: A low SoE supports a lack of consistent effects of prenatal or postnatal n-3 FA supplementation on the risk for AD/eczema and allergies and associations of biomarkers and intakes with these outcomes. A moderate SoE supports a lack of effect of prenatal maternal and postnatal infant n-3 FA supplementation on the risk for asthma and other respiratory illnesses. A low SoE supports inconsistent associations between n-3 FA exposures and risk for respiratory illnesses.

Adverse Events. A moderate SoE supports a lack of serious adverse events (AEs) among pregnant women and infants who consume supplemental n-3 FA or foods fortified with n-3 FA; a moderate SoE supports a lack of non-serious AEs, with the exception of an increased risk for mild gastrointestinal symptoms, among pregnant women and infants who consume supplemental n-3 FA.

Conclusions. Most studies identified for this report examined the effects of marine oil (or other combinations of DHA and EPA) supplements on pregnant or breastfeeding women or the effects of infant formula fortified with DHA plus arachidonic acid (AA). As with the original report, with the exception of small increases in birth weight and length of gestation, n-3 FA supplementation or fortification seems to have no consistent effects on peripartum maternal or infant health outcomes. Future RCTs need to assess standardized preparations of n-3 and n-6 FA, using a select group of clinically important outcomes, on populations with baseline n-3 FA intakes typical of those of most western populations.

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Executive Summary

The n-3 FA (including alpha linolenic acid [ALA], stearidonic acid [SDA], eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]) are a group of essential long-chain and very-long-chain polyunsaturated fatty acids (PUFA). Along with the n-6 FA (including linoleic acid [LA] and arachidonic acid [AA]), they are involved in the eicosanoid pathway and are incorporated into cell membranes. Eicosanoids (including AA, prostaglandins, thromboxanes, and leukotrienes) have wide ranges of physiologic effects and play a key role in inflammation regulation. ALA is the simplest n-3 FA from which all other n-3 FA are metabolically derived. ALA must come from the diet as it cannot be made by the body. ALA is found in plants, such as leafy green vegetables, nuts, and vegetable oils such as canola, soy, and flaxseed. SDA can be formed from ALA via $\Delta 6$ desaturase, the rate-limiting enzyme in the pathway. When SDA enters the metabolic pathway, it is rapidly converted to EPA. EPA can be converted to DPA and vice versa. The conversion rates from ALA to EPA or DHA are highly variable. Good sources of EPA and DHA in the diet include fish, other seafood, other marine sources (e.g., algae and phytoplankton), and organ meats.

A role for n-3 FAs in prenatal and postnatal growth and development and risk for certain chronic diseases has been suggested by a variety of evidence from prospective cohort studies and randomized controlled trials (RCTs). In 2002, the Institute of Medicine (IOM) considered the evidence inadequate to establish an estimated average requirement (EAR) for n-3 FAs.¹ Thus, in the absence of sufficient evidence, the IOM set only Adequate Intake values (AIs), based on current population intake in the apparent absence of deficiency symptoms.¹ The IOM set the following AIs for n-3 FA for healthy pregnant women and children:

Pregnant women: 1.4 grams(g)/day (d) of ALA

Infants (≤ 12 months): 0.5 g/d of n-3 FAs

Children (1 to 3 years): 0.7g/d of ALA

Children (4 to 8 years): 0.9 g/d of ALA

In 2004, at the request of the National Institutes of Health's (NIH) Office of Dietary Supplements (ODS), three Evidence-based Practice Centers (EPCs) conducted 11 systematic reviews (SRs) of the evidence for the health effects of n-3 FAs. Included among these SRs was one that encompassed outcomes related to the health of pregnant women and their children.² Maternal outcomes included gestational length, the risk for preterm birth, birth weight, intrauterine growth retardation (IUGR, small-for-gestational age, and low birth weight); birth length, head circumference, pregnancy hypertension and preeclampsia. Child health outcomes included neurological development; visual function in the first year of life; and various indices of cognitive development. Since the original review, many new studies and a number of SRs have examined the role of n-3 FAs in these outcomes. In addition, recent studies have suggested a potential role for n-3FAs in some related outcomes, e.g., the development of attention and working memory.³

¹ The use of an AI instead of an EAR indicates the need for more research to determine, with confidence, the mean and distribution of requirements for that nutrient; AIs are based on much less data and more scientific judgment than are EARs.

Scope and Key Questions

Scope of the Review

The current systematic review has four aims: 1) to update the original review on the topic of the effects of n-3 FAs on maternal and child outcomes,² 2) to identify the literature for several additional outcomes of interest (see below) not included in the original review; 3) to include prospective observational studies that were excluded from the original report when two or more RCTs were identified for an outcome of interest; and 4) to use this new review to collect additional information such as baseline intakes of or exposures to n-3 FAs and associations between exposure dose and response that would enhance the usefulness of this report for policy and clinical applications. Therefore, it is of interest to systematically compare results across different exposure/intervention products and study types (e.g., interventional vs. prospective cohort studies), and to account for differences in background n-3 FA intake.

This update includes the addition of seven new outcomes: (maternal) ante- and postnatal depression, and pediatric attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), learning disabilities, atopic dermatitis, allergies, and respiratory disorders, specifically looking at the risk for (or prevention of) these conditions in otherwise healthy individuals and their offspring, rather than the efficacy of n-3 FA in treating affected individuals.

Key Questions

The key questions address both issues of efficacy (i.e., causal relationships from trials) as well as associations (i.e., prospective cohort study results and outcomes or risk factors from RCTs for which the randomization may not be applicable). Compared with the key questions from the 2005 report, they expand the scope of the review to include additional maternal and child outcomes, as noted above and described below (shown in bold face).

Key Question 1: Maternal Exposures

- What is the efficacy of maternal interventions involving—or association of maternal exposures to—n-3 FAs (EPA, DHA, EPA+DHA, DPA, ALA, SDA, or total n-3 FA) on the following:
 - duration of gestation in women with or without a history of preterm birth (less than 37 weeks gestation),
 - incidence of preeclampsia/eclampsia/gestational hypertension in women with or without a history of preeclampsia/eclampsia/gestational hypertension
 - Incidence of birth of small-for-gestational age human infants
 - **Incidence of ante- and/or postnatal depression in women with or without a history of major depression or postpartum depression**
- What are the associations of maternal biomarkers of n-3 intake during pregnancy and the outcomes identified above?

- What are the effects of potential confounders or interacting factors (such as other nutrients or use of other supplements, or smoking status)?
- How is the efficacy or association of n-3 FA on the outcomes of interest affected by the ratio of different n-3 FAs, as components of dietary supplements or biomarkers?
- How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on the outcomes of interest?
- Is there a threshold or dose-response relationship between n-3 FA exposures and the outcomes of interest or adverse events?
- How does the duration of the intervention or exposure influence the effect of n-3 FA on the outcomes of interest?

Key Question 2: Fetal/childhood exposures

- What is the influence of maternal intakes of n-3 fatty acids or the n-3 fatty acid content of maternal breast milk (with or without knowledge of maternal intake of n-3 FA) or n-3 FA-supplemented infant formula or intakes of n-3 FA from sources other than maternal breast milk or supplemented infant formula on the following outcomes in term or preterm human infants?
 - Growth patterns
 - Neurological development
 - Visual function
 - Cognitive development
 - **Autism**
 - **Learning disorders**
 - **ADHD**
 - **Atopic dermatitis**
 - **Allergies**
 - **Respiratory illness**
- What are the associations of the n-3 FA content or the n-6/n-3 FA ratio of maternal or fetal or child biomarkers with each of the outcomes identified above?

Key Question 3: Maternal or childhood adverse events:

- What are the short and long term risks related to maternal intake of n-3 fatty acids during pregnancy or breastfeeding on
 - Pregnant women
 - Breastfeeding women
 - Term or preterm human infants at or after birth
- What are the short and long term risks associated with intakes of n-3s by human infants (as maternal breast milk or infant formula supplemented with n-3 FA)?
- Are adverse events associated with specific sources or doses?

Methods

The present review evaluates the effects of—and the associations between—n-3 FAs intakes (including EPA, DHA, DPA, ALA, SDA, and n-3 biomarkers) and maternal and child health outcomes. The Evidence-based Practice Center (EPC) conducted the review based on a systematic review of the published scientific literature using established methods as outlined in the Agency for Healthcare Research and Quality (AHRQ)’s Methods Guide for Comparative Effectiveness Reviews.⁴

This review is conducted in parallel with a systematic review of n-3 FA and cardiovascular disease, conducted by another EPC. Several aspects of the reviews are being coordinated, including eligibility criteria regarding interventions and exposures, search strategies, structure of the reviews, and assessments of the studies’ risk of bias, strength of the bodies of evidence, and abstraction of study characteristics needed to assess causality.

We convened a Technical Expert Panel (TEP) to help refine the research questions and protocol. We discussed the key questions, analytic framework, study eligibility criteria, literature search, and analysis plans.

Literature search

Search strategy

We modified the existing search strategies from the original report (see Appendix A) to include a complete set of terms for the new outcomes of interest based on searches we have conducted on these topics for previous reviews and consultation with colleagues. We conducted literature searches in Medline (Pubmed), Embase, the Cochrane Collection, Web of Science and CAB. For the topics of depression; ADHD; autism; and cognitive, neurological, and visual function development, we searched PsychInfo. We did not search for unpublished (grey) literature; however a notice was published in the Federal Register requesting unpublished data from manufacturers of omega-3 fatty acid-fortified infant formulae and dietary supplements. Searches for all topics began with the year 2000. For the newly added topics, we “reference mined” articles that we identified to determine whether any studies conducted and published prior to 2000 should be obtained and included. Studies in the original report deemed eligible for pooling with newly identified studies were included, as were prospective cohort and nested case control studies excluded from the original report that met current inclusion criteria.

[The search will be updated upon submission of the draft report for peer and public review.]

Inclusion and exclusion criteria

The current eligibility criteria are mostly similar to the criteria used in the original 2005 review. The populations are expanded to accommodate the expanded outcomes of interest. The interventions and exposures remain the same as those in the original report, with the addition of two n-3 FA (DPA and SDA). Included study designs have been modified slightly.

The Eligibility Criteria are outlined here according to the PICOT framework, with indications of the key questions to which they apply.

- **Population(s):**
 - Key Question (KQ) 1(Maternal exposures and outcomes)
 - Healthy pregnant women (for outcomes of birth weight, intrauterine growth restriction/small for gestational age, duration of gestation, risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
 - Pregnant women with a history of pre-eclampsia, eclampsia, or pregnancy hypertension (only for outcome of risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
 - Pregnant women with a history of major depressive disorder or postpartum depression (only for the outcome of risk for peripartum depression)
 - Key Question 2 (In utero and postnatal (through the first year of life) exposures and outcomes)
 - Healthy preterm or full term infants of healthy women/mothers whose n-3 fatty acid exposures were monitored during pregnancy
 - Breastfed infants of healthy mothers whose n-3 fatty acid exposure was monitored and/or who participated in an n-3 fatty acid intervention during breastfeeding beginning at birth
 - Healthy preterm or full term infants with and without family history of respiratory conditions (for outcomes related to atopic dermatitis, allergy, respiratory conditions) of mothers whose n-3 exposures were monitored during pregnancy and/or breastfeeding
 - Healthy children or children with a family history of a respiratory disorder, a cognitive or visual development disorder, autism spectrum disorder, ADHD, or learning disabilities, age 0 to 18 years who participated in an n-3 fatty acid-supplemented infant formula intervention or an n-3 supplementation trial during infancy
 - Key Question 3 (Adverse events associated with n-3 interventions)
 - Healthy pregnant women or pregnant women in the other categories described above
 - Offspring of women enrolled in an n-3 fatty acid intervention during pregnancy
 - Offspring of women whose exposure to n-3 fatty acids was assessed during pregnancy
 - Children whose exposure to n-3 fatty acids (through breast milk, infant formula, or supplementation) was monitored during the first year of life
- **Interventions/Exposures:**
 - Interventions (KQ1, 2, 3 unless specified):

- N-3 fatty acid supplements (e.g., EPA, DHA, ALA, singly or in combination;
 - N-3 fatty acid supplemented foods (e.g., eggs) with quantified n-3 FA content
 - High-dose pharmaceutical grade n-3 fatty acids, e.g., Omacor®, Ropufa®, MaxEPA®, Efamed, Res-Q®, Epagis, Almarin, Coromega, Lovaza®, Vascepa® (icosapent ethyl)
 - Exclude doses of more than 6g/d, except for trials that report adverse events
 - N-3 fatty acid fortified infant formulae (KQ2,3)
 - E.g., Enfamil® Lipil®; Gerber® Good Start DHA & ARA®; Similac® Advance®
 - N-3 FA fortified follow-up formulae
 - Exclude parenterally administered sources
 - Marine oils, including fish oil, cod liver oil, menhaden oil, and algal with quantified n-3 FA content
 - Algal or other marine sources (e.g., phytoplankton) of omega-3 fatty acids with quantified n-3 content
- Exposures (KQ1,2)
 - Dietary n-3 fatty acids from foods if concentrations are quantified in food frequency questionnaires
 - Breast milk n-3 fatty acids (KQ2)
 - Biomarkers (EPA, DHA, ALA, DPA, SDA), including but not limited to the following:
 - Plasma fatty acids
 - Erythrocyte fatty acids
 - Adipocyte fatty acids.
- **Comparators:**
 - Inactive comparators:
 - Placebo (KQ1, 2, 3)
 - Non-fortified infant formula (KQ2)
 - Active comparators
 - Different n-3 sources
 - Different n-3 concentrations (KQ1, 2, 3)
 - Alternative n-3 fortified infant formulae (KQ2)
 - Soy-based infant formula (KQ2)
 - Diet with different level of Vitamin E exposure
- **Outcomes:**
 - Maternal outcomes (KQ1)
 - Blood pressure control
 - Incidence of gestational hypertension
 - Maternal blood pressure
 - Incidence of pre-eclampsia, eclampsia
 - Peripartum depression
 - Incidence of antepartum depression⁵

- Incidence of postpartum depression, e.g.,
 - Edinburgh Postnatal Depression scale
 - Structured Clinical Interview (SCI)
- Gestational length
 - Duration of gestation
 - Incidence of preterm birth
- Birth weight
 - Mean birth weight
 - Incidence of low birth weight/small for gestational age
- Pediatric Outcomes (KQ2)
 - Neurological/visual/cognitive development
 - Visual development, e.g.,
 - Visual evoked potential acuity
 - Behavioral visual acuity testing
 - Teller's Acuity Card test and others
 - Electroretinography
 - Cognitive development, e.g.,
 - Bayley's mental development index
 - Knobloch, Passamanick, and Sherrard's developmental Screening Inventory scores
 - Fagan Test of Infant Intelligence
 - Stanford-Binet IQ
 - Receptive Vocabulary
 - Peabody Picture Vocabulary Test-Revised
 - Neurological development
 - Electroencephalograms (EEGs) as measure of maturity
 - Psychomotor developmental index from Bayley's scales
 - Neurological/movement impairment assessment
 - Active sleep, quiet sleep, sleep-wake transition, wakefulness
 - Nerve conduction test
 - Latency Auditory evoked potential
 - Risk for ADHD
 - Validated evaluation procedures
 - E.g., Wechsler Intelligence Scale for Children,
 - Behavioral rating scales, e.g., Connors, Vanderbilt, and Barkley scales
 - Risk for Autism spectrum disorders
 - Validated evaluation procedures
 - E.g., Modified Checklist of Autism in Toddlers
 - Risk for learning disabilities
 - Validated evaluation procedures
 - Risk for atopic dermatitis
 - Risk for allergies
 - Validated allergy assessment procedures, preferably challenge (skin prick test or validated blood tests accepted)

- Incidence of respiratory disorders
 - Spirometry in children 5 and over (peak expiratory flow rate [PEFR] and forced expiratory volume in 1 second [FEV₁])
 - Key Question 3: Adverse effects of intervention(s)
 - Incidence of specific adverse events reported in trials by study arm
- **Timing:**
 - Duration of intervention or follow-up
 - Key Question 1,3 (maternal interventions/exposures):
 - Interventions implemented anytime during pregnancy but preferably during the first or second trimester
 - Followup duration is anytime during pregnancy (for maternal outcomes of pre/eclampsia or maternal hypertension); term (for outcomes related to birth weight, duration of pregnancy); or within the first 6 months postpartum (for the outcome of postpartum depression)
 - Key Question 2, 3 (infant exposures):
 - Interventions implemented within one month of birth or exposures measured within 1 month of birth
 - Followup duration is 0 to 18 years
- **Settings:**
 - Community-dwelling individuals seen by primary care physicians or obstetricians in private or academic medical practices (KQ1, 3)
 - Community dwelling children seen in outpatient health care or educational settings (KQ2, 3)

We limited the study designs of interest to RCTs of any size, and to prospective cohort studies, and nested case control studies of sample size 250 or greater (cross-sectional, retrospective cohort, and case study designs were excluded; studies must have measured intake/exposure prior to outcome). Only peer-reviewed studies published in English language were included. Unpublished studies were not included.

Study selection

The DistillerSR software package was used to manage the search outputs, screening, and data abstraction. Title/abstract screening was conducted in duplicate). All title selections were accepted without reconciliation for further full-text review. Second-level screening of full text articles was conducted by two reviewers and differences reconciled (the project leaders settle disagreements, if needed).

Data extraction

Accepted studies underwent single abstraction of study-level data and risk-of-bias assessment in Distiller, with audit by an experienced reviewer. Outcome data were abstracted by a biostatistician and audited by an experienced reviewer. We re-extracted data from studies included in the original report that are to be included in new pooled analyses as needed.

Methodological quality (risk of bias) assessment of individual studies

We assessed the methodological quality of each study based on predefined criteria. Risk of bias among RCTs was assessed using the Cochrane Risk of Bias tool,⁶ which evaluates risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias. Risk of bias among observational studies was assessed using questions relevant for prospective studies from the Newcastle-Ottawa tools.⁷ Both tools were supplemented with nutrition-specific items in consultation with the TEP (e.g., those related to uncertainty of dietary assessment measurements and compliance).⁸⁻¹⁰

Data Synthesis/Analysis

We considered meta-analyses when there were at least three trials with similar intervention (i.e. DHA, DHA+EPA, DHA+AA), follow-up time (i.e. birth, 12 months of age), and population (i.e. pregnant women, term infants, preterm infants). For trials that had groups with the same intervention but with varying doses, we averaged the outcome across doses for the main analysis. Forest plots were provided for random effects meta-analysis. We used the Hartung-Knapp-Sidik-Jonkman method for our random effects meta-analysis.¹¹⁻¹³ It has been shown that the error rates from this method are more robust than the previously used DerSimonian and Laird method.¹⁴ Heterogeneity was assessed using the I² statistic.¹⁵ All statistical analyses were performed in R 3.2.0.¹⁶

New trial results were added to original meta-analyses, when appropriate, based on similarity of participants, interventions (including doses), and outcomes.⁴

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

The strength of evidence was assessed for each outcome and exposure type using the method outlined in the AHRQ Methods Guide,⁴ in which the body of evidence for each outcome is assessed based on the following dimensions: study limitations (risk of bias), reporting bias, consistency (within and across study designs), directness (of study outcome measures), and precision, as well as the number of studies by study design. Based on these assessments, we assigned a strength of evidence rating (i.e., insufficient, low, moderate, or high level of evidence). The data sources, basic study characteristics, and each strength-of-evidence dimensional rating were summarized in a “Summary of Evidence Reviewed” table detailing our reasoning for arriving at the overall strength of evidence rating. Peer Review and Public Commentary

A draft version of this report [is being] reviewed by a panel of expert reviewers, including representatives from [pending] and the general public. The reviewers included experts in [pending]. These experts were either directly invited by the EPC Program or offered comments through a public review process. Revisions of the draft [will be] made, where appropriate, based on their comments. The draft and final reports [will] also reviewed by AHRQ. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

For this systematic review, we identified 74 RCTs (in 75 publications) and 43 eligible prospective longitudinal studies and nested case-control studies that were eligible for inclusion based on the prespecified inclusion criteria. Most of the RCTs evaluated the effects of marine oil supplements on weight gain during pregnancy (risk for low birthweight) and length of gestation (risk for preterm birth) or the effects of DHA with or without AA as supplements or added to infant formulas on infant neural and cognitive development. Most observational studies assessed the association between the status of particular n-3 FA and developmental outcomes.

We summarize the results of our review below by the outcomes of interest (maternal outcomes, childhood outcomes, adverse events), and within each outcome, by the target population for the intervention (e.g., pregnant women, preterm infants, term infants) where relevant, and further by the intervention or exposure.

Maternal Exposures and Outcomes

Length of Gestation and the Risk for Preterm Birth

The original report found inconsistent effects of prenatal maternal supplementation with DHA on length of gestation or the risk for preterm birth and a consistent finding of no effects of prenatal maternal supplementation with EPA+DHA among a large number of RCTs. The current report also identified similar findings for these outcomes in RCTs.

For the current report, pooled analysis of 10 RCTs among healthy pregnant women found a significant increase in length of gestation among mothers who received algal DHA or DHA-enriched fish oil (WMD +0.36 week [95% CI 0.01, 0.71]) compared to placebo. Pooled analysis of six RCTs showed no significant effect of DHA or DHA-enriched fish oil on the risk for preterm birth.

Pooled analysis of five RCTs showed that maternal fish oil supplementation (EPA+DHA) had no significant effects on length of gestation. Pooled analysis of nine RCTs (in four publications) found no effects of EPA+DHA supplementation (either as non-enriched fish oil or purified DHA plus EPA supplements) on the incidence of preterm birth.

Prospective studies are sparse and found no consistent associations of maternal exposures with outcomes related to length of gestation or preterm birth.

Birthweight and the Risk for Low Birth Weight or Small-for-Gestational Age Birth

The original report did not find a significant effect of maternal n-3FA supplementation on the risk for low birth weight or SGA or a clear association of any maternal biomarkers with risk for low birth weight or birth weight itself.

For the current report, we found a moderate level of evidence that maternal supplementation with DHA may increase birth weight, and a low level of evidence that maternal supplementation with EPA+DHA may not have significant effects on birth weight. Pooled analysis of 11 RCTs showed significantly higher birth weights among infants (mixed term and preterm) whose mothers received algal DHA or DHA-enriched fish oil compared with placebo (WMD [95% CI]=103.13 [6.83-199.43] grams). Pooled analysis of five RCTs found no effect of maternal EPA+DHA supplementation on infant birth weight. One RCT assessing the effects of ALA on infant birth weight showed no effects. These findings are consistent with prospective studies, found that higher maternal blood DHA concentrations were associated with higher birth weight .

There is also a low level of evidence that maternal supplementation with EPA+DHA may not have significant effects on risk for delivering a low birth weight infant among at-risk pregnant women, but the evidence is insufficient for the effects of maternal supplementation with DHA on risk for delivering a low birth weight infant among healthy pregnant women. Pooled analysis of four RCTs showed no significant effects of DHA+EPA supplementation (doses ranged from 2.0 to 3 g/d) on the incidence of small for gestational age between DHA+EPA supplementation and control groups (OR [95% CI]=1.00, CI[0.70, 1.43]) Pooled analysis of three RCTs identified for the current study that assessed the effects of DHA alone or DHA-enriched fish oil showed no significant effects on the risk for delivering a low birth weight infant among women who were not at risk. Observational studies were sparse and showed mostly no associations between n-3FA intake or biomarkers and these outcomes.

Risk for Antenatal and Postnatal Depression

The outcome of risk for antenatal and postnatal depression was a new one for this review. Three RCTs that assessed the effects of prenatal supplementation with DHA alone, DHA+AA, or EPA-enriched fish oil or postnatal supplementation with DHA alone found no effects on risk of developing perinatal depression among healthy pregnant women. Prospective studies found inconsistent associations of maternal n3FA levels and risk of developing perinatal depression.

Risk for Gestational Hypertension or Preeclampsia

The original report found no consistent effect of maternal supplementation with n-3FA on the risk for gestational hypertension or preeclampsia. Pooling one study identified for the current report and two studies from the original report that randomized high-risk women to DHA supplements or placebo resulted in a non-significant decrease in the risk for gestational hypertension or preeclampsia among the DHA-treated women (OR 0.94[0.66, 1.34], $I^2=0\%$ (n=2,818); pooling studies of women not at high risk that were randomized to fish oil or placebo also showed no effect (OR 1.04 [0.76 , 1.42], $I^2=0\%$).

Childhood Outcomes

Postnatal Growth Patterns

The original report found no or inconsistent effects of maternal supplementation or infant formula fortification on postnatal growth patterns. For the current report, pooled analysis of five RCTs of prenatal (maternal) supplementation alone with DHA and EPA or fish oil (no postnatal supplementation) showed no significant effects on weight, length, or head circumference at 18 months.

Pooled analysis of three studies of fortification of infant formula with DHA and AA also showed no effects on postnatal weight gain and length at 4 months among preterm infants.

Neurological Development

The original report found no consistent effect of maternal or infant supplementation with n-3 FA on neurological developmental outcomes and inconsistent associations with biomarkers. Likewise, 11 RCTs identified for the current report found no consistent effects of n-3 FA alone or in combination with AA or LA on any of these outcomes compared with placebo. Two studies reported a positive effect of formula supplemented with DHA and AA on Bayley's Psychomotor

Development Index (PDI) scores (an index of motor development) in preterm infants at 12 and 18 months, and two RCTs reported positive effects on brainstem maturation but the remaining studies reported mixed effects on gross motor control in term infants supplemented with DHA and similarly mixed effects of DHA plus AA on other outcomes.

Visual Function

The original report found inconsistent effects of maternal and infant supplementation with n-3 FA on visual development, and differences between effects on behavioral measures of visual function and effects on electrophysiological measures (visual evoked potentials [VEP]). The current report identified one RCT that found that DHA supplementation of breast-feeding mothers resulted in improvement in one VEP outcome (transient VEP amplitude) at 4 and 8 months of age but not at 5 years of age; No differences were seen in other VEP measures, including sweep VEP and transient VEP latency, and no differences were seen using behavioral measures at any age. Another RCT reported that supplementing preterm infants with a DHA-enriched fish oil did not influence visual acuity at 2 or 4 months. One new RCT and five RCTs from the original report show no significant effect of supplementing preterm infants with DHA plus AA on infant visual acuity at 4 months but pooling one new RCT and three RCTs from the original report showed a significant effect of DHA plus AA at 12 months. In full-term infants, one new RCT and two RCTs from the original report suggest a possible long-term effect of DHA supplementation on visual acuity but the findings for different outcome measures are inconsistent. Feeding full-term infants with a DHA plus AA-fortified supplement also showed signs of a beneficial effect on visual acuity maturation in three new studies, eight studies from the original report, and a recent MA that included studies from both the current and original report.

Cognitive Development

The original report found inconsistent effects of n-3 FA supplementation on cognitive development. Eight studies identified for the current report on supplementation of pregnant women (including one followup from the original report) showed no significant effects on cognitive outcomes in infants or children. Six RCTs identified for the current report on supplementation of breastfeeding women with fish oil, cod liver oil, or high-DHA algal oil (two studies each) showed no significant effects on any cognitive outcomes among infants or children (born preterm or term) at 9 months to 7 years of followup. Six RCTs identified for the current report showed inconsistent effects of n-3 FA fortified commercial infant formula or administration of fish oil supplements on cognitive developmental outcomes among infants born preterm. Four RCTs identified for the current report found inconsistent effects of n-3 FA fortified formula on cognitive outcomes among infants and children born at term: one study reported higher MDI scores at 18 months among toddlers who had received fortified formula. Among six observational studies identified for the current report, almost no associations between biomarker levels of n3FAs and cognitive outcomes were noted. In one observational study that controlled for 18 potential confounders, low levels of AA in erythrocytes of pregnant women were associated with lower performance IQ; high levels of adrenic acid were associated with lower verbal IQ; and low levels of DHA were associated with lower verbal and full scale IQ at age 8; however, the authors caution that the effect sizes were small. Because of heterogeneity, no

studies identified for the current report could be pooled with each other or with studies from the original report.

Risk for Autism, Learning Disorders, and Attention Deficit Hyperactivity disorder

Developmental outcomes newly included for the current report were the risk for Autism Spectrum Disorders (ASD), Learning Disorders, and Attention Deficit Hyperactivity Disorder (ADHD). Only one observational study was identified that assessed the association between n-3 FA intake and the risk for ASD; this study found no association. No studies were identified that explicitly assessed the association between n-3 FA intakes or exposures and the risk for learning disorders or ADHD.

Allergy, Atopic Dermatitis, and Respiratory Conditions

Additional outcomes newly included in the current report were risks for atopic dermatitis/eczema, risks for allergies, and risks for respiratory illnesses, including asthma. A number of studies were conducted in mothers or infants at high familial risk for allergies or asthma.

Atopic dermatitis/eczema: Four prenatal and three postnatal studies showed no significant effects of maternal n-3 FA supplementation on the risk for atopic dermatitis/eczema. Only one of the seven prospective observational studies found higher concentrations of breast milk n-3 FA to be significantly associated with a lower risk of developing atopic dermatitis; the remaining six studies found no associations between n-3 FA exposures (measured through maternal dietary intake or breast milk composition) and risk for atopic dermatitis/eczema; however studies that assessed the association of biomarkers with this risk observed inconsistent associations of risk for atopic dermatitis with plasma levels of DHA, erythrocyte EPA, AA levels, and EPA/AA ratios. One of three prospective observational studies of n-3 FA biomarkers (in cord blood or maternal blood sample) found decreased risk of eczema and increasing AA levels, with null findings for the remaining two studies.

Food Allergies: Metaanalysis of three RCTs that assessed the effect of maternal supplementation with DHA plus EPA showed a nonsignificant reduction in the risk for food allergies. Use of infant formula fortified with DHA and AA or tuna oil or administration of fish oil capsules did not influence the risk for allergies. Prospective observational studies showed no consistent associations of maternal or infant n-3 FA exposures with risk for allergies.

Respiratory illness/Asthma: Among seven RCTs that assessed the effect of prenatal n-3 FA supplementation on the risk for respiratory illnesses (including wheeze, asthma, persistent cough, inflammation, and respiratory infections), only two reported significant effects—decreases in the risk for asthma—but these effects were not consistent over time. A metaanalysis of three postnatal interventions that assessed the effects of DHA-fortified formula on risk for wheeze found no significant effect. Prospective observational studies and biomarker studies reported inconsistent associations between various postnatal n-3 FA and n-6 FA exposures and risk for respiratory illnesses, with some studies showing an association between lower DHA, EPA, or total n-3 FA exposures or higher n-3 FA to n-6 FA ratios and lower risk for respiratory conditions (wheeze or asthma) but some studies of the same exposures showing no effects.

Adverse Events

The original report identified 21 RCTs that reported on adverse events with n-3 FA supplementation in pregnant women, breastfeeding mothers, and preterm and term infants. Overall they found that n-3 FA supplements and fortified formulas were well tolerated. Pregnant and breastfeeding women reported no serious adverse events, and adverse events in these groups were limited to mild GI symptoms. Among both preterm and term infants, adverse events were largely limited to GI symptoms also, with most serious adverse events attributable to morbidities associated with prematurity.

The current report identified 18 RCTs that reported on adverse events. The profile of both non-serious and serious adverse events in this report was identical to that of the original report. None of the observational studies identified for the current report described adverse events.

Mercury exposure issues

Discussion

Overall Summary and Strength of Evidence

As with the original report, most of the studies identified for the current report assessed the effects of n-3 FA interventions (or associations with exposures) on birth weight (or risk for low birth weight or intrauterine growth retardation), gestational length (or risk for preterm birth), and cognitive outcomes among children. Among studies reporting on the same outcomes, results were often inconsistent across studies.

The current study identified a small but significant effect of DHA supplementation of pregnant women on the length of gestation, strengthening a non-significant finding in the original report. As in the original report, the current report found no effect of DHA- or other n-3 FA supplementation on the risk for preterm birth, and observational studies provided inconsistent results. The difference in findings with respect to length of gestation (a continuous variable) and the risk for preterm birth (a dichotomous variable) is unclear but may be attributable to several factors. Many more studies assessed length of gestation than assessed risk for preterm birth. The effect size for the increase in gestational length may not have been large enough to translate to an observable decrease in risk for preterm birth. Alternatively, the exclusion of preterm infants from some studies that assessed effects of supplementation on length of gestation could have skewed the results, or the populations enrolled in studies that assessed risk for preterm birth may have had sufficient baseline n-3 FA status. Too few studies assessed baseline status to examine this possibility.

The current study also found a significant effect of maternal DHA supplementation on birthweight in a pooled analysis of three studies, in contrast to the original report, which saw no effect from pooling two studies. Similar to the original report, a pooled analysis for the current report saw no significant effect of supplementation with DHA on the risk for low birth weight among women who were not at risk due to a prior low-birth-weight pregnancy. Reasons for the difference in these two outcomes may be similar to those posited for length of gestation. In addition, a study by Makrides and colleagues included in this review reported that the increase in birth weight that resulted from DHA supplementation was largely attributable to the increase in gestational age at birth. {#3069}

The findings for the remainder of the maternal outcomes (perinatal depression, gestational hypertension/preeclampsia) and the childhood outcomes (visual function, neurodevelopment, cognitive development, autism spectrum disorder, attention deficit hyperactivity disorder,

learning disorders, atopic dermatitis/eczema, allergy, and respiratory disorders) were too inconsistent across studies as well as within studies at different follow-up time points to draw any conclusions.

Too few studies assessed the effects of increasing doses of n-3 FA using similar populations and outcome measures to enable dose-response or threshold estimation.

Few studies stratified outcomes according to risk groups, so it was usually not possible to assess whether the effectiveness of omega-3 interventions depended on level of risk. In addition, no studies stratified outcomes by baseline n-3 FA status, so it is not possible to assess whether adequacy of n-3 FA status might account for differences in outcomes across (or lack of outcomes within) studies.

Table A summarizes the findings for which we identified a low, moderate, or high strength of evidence (SoE) for an effect or no effect of n-3 FA.

Table A. Conclusions with Strength of Evidence for an Effect or Lack of Effect

Outcome	Intervention/Exposure	Study Design	Strength of Evidence	Conclusion
Maternal outcomes				
Length of gestation	Algal DHA or DHA-enriched fish oil supplementation of pregnant women	RCTs	Low	Increase in gestational length compared with placebo
Length of gestation	EPA+DHA fish oil supplementation of pregnant women	RCTs One observational study	Low	No significant effects on gestational age compared with placebo
Risk for Preterm birth	Algal DHA or DHA-enriched fish oil supplementation of pregnant women	RCTs	Low	No change in risk for preterm birth compared with placebo
Risk for Preterm birth	EPA+DHA fish oil supplementation of pregnant women	RCTs One observational study	Low	No significant effects on the incidence of preterm birth compared with placebo
Birth weight	Algal DHA or DHA-enriched fish oil supplementation of pregnant women	RCTs Small number of observational studies	Moderate	Increase in birth weight compared with placebo
Birth weight	EPA+DHA fish oil supplementation of pregnant women	RCTs and observational studies	Low	No significant effects on birth weight compared with placebo
Low birth weight	Algal DHA or DHA-enriched fish oil supplementation of pregnant women	RCTs and observational studies	Low	No significant effects on risk of low birth weight compared with placebo
SGA / IUGR	EPA+DHA supplementation of at risk pregnant women	RCTs One observational study	Low	No significant effects on SGA/IUGR compared with placebo
Gestational hypertension	DHA supplementation of normal-risk pregnant women	RCTs	Low	Lack of effect on risk for gestational hypertension in normal risk women
Gestational hypertension	DHA supplementation of high-risk pregnant women	RCTs	Moderate	Lack of effect on risk for gestational hypertension among high-risk women
Peripartum depression	Prenatal DHA or DHA+AA	RCTs Observational studies	Low	Lack of effect on risk for peripartum depression
Infant and Child Outcomes				
Postnatal growth patterns	Fish oil or DHA+EPA supplementation of pregnant women	RCTs	moderate	Lack of effect on postnatal growth patterns among healthy term infants
Postnatal growth patterns	Supplementation of breastfeeding women with any n-3FA	RCTs	Low	Lack of effect on postnatal growth patterns
Postnatal growth patterns	Feeding preterm or term infants with infant formula fortified with DHA+AA	RCTs	Low	Lack of effect on postnatal growth patterns

Outcome	Intervention/Exposure	Study Design	Strength of Evidence	Conclusion
Visual acuity	Supplementation of pregnant women with DHA-enriched fish oil	RCTs	Low	No effect on development of visual acuity in infants.
Visual acuity	Feeding preterm and term infants with DHA plus AA-fortified infant formula	RCTs	Low	Positive effects on development of visual acuity in infants assessed at 12 months.
Neurological development	Supplementation of pregnant women with DHA-enriched fish oil	RCTs	Low	Inconsistent effects on any measure of neurological development
Cognitive development	Supplementation of pregnant women with DHA	RCTs	Low	Inconsistent effects on any measure of cognitive development
Cognitive development	Supplementation of pregnant women with other n-3 FA	RCTs	Moderate	Lack of effects on any measure of cognitive development
Cognitive development	Supplementation of breastfeeding women with DHA+EPA	RCTs	Low	Inconsistent effects on any measure of cognitive development
Atopic dermatitis/ eczema	Supplementation of pregnant women with any n-3 FA or exposures as assessed by biomarkers	RCTs and observational studies	Low	Inconsistent effects on risk for atopic dermatitis/eczema
Atopic dermatitis/ eczema	Supplementation of breastfeeding mothers or infants through formula fortification with any n-3 FA or exposure as assessed with biomarkers	RCTs and observational studies	Low	Inconsistent effects on risk for atopic dermatitis/eczema
Allergies	??			
Asthma and other respiratory illnesses	Supplementation of pregnant women with any n-3 FA	RCTs	Moderate	Lack of effect on the risk for asthma and other respiratory illnesses
Asthma and other respiratory illnesses	Supplementation of breastfeeding women with any n-3 FA or fortification of infant formula with n-3 FA	RCTs	Moderate	lack of effect on the risk for asthma and other respiratory illnesses
Asthma and other respiratory illnesses	n-3 FA exposures of pregnant women or infants	Observational studies	Low	Inconsistent associations with risk for respiratory illnesses.
Adverse events				
Maternal adverse events Non-serious	Supplementation of pregnant or breastfeeding women with n-3 FA in the form of fish oil	RCTs	Moderate	Increased risk for mild gastrointestinal symptoms but no other consistent non-serious adverse events
Maternal adverse events serious	Supplementation of pregnant or breastfeeding women with n-3 FA in	RCTs	Moderate	No increase in risk for serious adverse events

Outcome	Intervention/Exposure	Study Design	Strength of Evidence	Conclusion
	the form of fish oil			
Infant adverse events non-serious	Supplementation of healthy term infants or preterm infants with n-3 FA in the form of fish oil alone or added to infant formula	RCTs	Moderate	Increased risk for mild gastrointestinal symptoms but no other consistent non-serious adverse events
Infant adverse events serious	Supplementation of healthy term infants with n-3 FA in the form of fish oil	RCTs	Moderate	No increase in risk for serious adverse events
Infant adverse events serious	Supplementation of preterm infants with n-3 FA in the form of fish oil	RCTs	Low	No change in risk for serious events associated with preterm birth

Limitations

Within each category of analysis (by outcome, target of intervention, n-3 FA, and study design), studies we identified for this review (like the studies included in the original review) diverged greatly with respect to the sources, doses, and durations of interventions; definitions or tests used to measure outcomes; and followup times. For outcomes such as visual, neurological, and cognitive development, by necessity, the tests used over time (in studies with multiple followups) changed to match maturity level. As a result, it was challenging to identify groups of studies that were sufficiently similar to pool, even with studies from the original report. In addition, many RCTs employed and reported the results of numerous outcome measures, which were often internally inconsistent or showed no apparent pattern over time. The majority of studies did not find statistically significant findings. Only a small number of observational studies that were excluded from the original report met the inclusion criteria for the current report, and the observational studies identified for the current report seldom assessed outcomes that were similar to those assessed in RCTs.

Overall, both RCTs and observational studies included in this review had numerous quality concerns that increased the risk for bias. Across RCTs, the most common risk-of-bias limitation was a lack of intention-to-treat analyses (47 percent of the included RCTs). Of included RCTs, 35 percent failed to describe allocation concealment sufficiently to determine whether it was adequate (and many studies failed to describe recruitment methods). Blinding of study participants contributed only slightly to potential risk of bias because participants were usually infants or children and outcomes were usually clinically apparent or assessed in a clinical laboratory. Twenty-seven percent of RCTs were at risk of attrition bias due to overall dropout rates greater than 20 percent, although most studies reported similar dropout rates between groups. Although 87 percent of the included RCTs reported similar baseline demographic characteristics between groups, but 51 percent did not report baseline n-3 FA intake or status. This omission is a critical concern because baseline n-3 FA status likely affects response to changes in n-3 FA intake.

Across observational studies, the most common risk of bias limitation was the lack of representativeness of the cohorts to the population of interest: 37 percent were judged to be select populations or only somewhat representative. In most cases, these populations were described as having high intakes of fish; in several cases, the populations were at high risk for the outcome of interest or another condition. Another reporting inadequacy related to the ranges and distribution of n-3 FA exposures. Of included observational studies, most of the n-3 FA dietary intake assessments included only dietary sources (not n-3 FA supplements). This issue does not affect the quality of biomarker data; however, so many different n-3 FA biomarkers were investigated across studies, that it was impossible to make comparisons.

Few studies reported adverse events, but among the 18 studies that did report adverse events, 55 percent did not predefine or prespecify adverse events to be queried, and none used a recognized categorization system to prespecify or sort categories or levels of intensity of adverse events reported. Only 30 percent reported an active mode of collection of adverse event information, and of the studies that reported serious adverse events (or lack thereof), most did not define “serious adverse event.” Of additional concern, studies of preterm infants often comingled morbidities associated with prematurity (such as bronchopulmonary dysplasia and retinopathy of prematurity) and adverse events that might be associated with the intervention.

Only one study that met inclusion criteria considered whether mercury exposure could account for the findings on the effects of fish oil intake, but the findings were equivocal.

Understandably, a number of the RCTs were conducted in women at risk for premature birth, gestational hypertension, a low birth weight infant, or women with a personal or family history of allergy or asthma. However, most observational studies examining the associations between dietary n-3 FA intake or biomarkers of n-3 FA intake and birth, respiratory, allergy, or developmental outcomes were conducted in generally healthy populations. Most RCTs were also small in size, although most reported doing power calculations. Observational studies that enrolled fewer than 250 were excluded by design.

Study interventions tended to be highly heterogeneous. Studies that labeled themselves as studies of DHA alone often included some amount of EPA as well as n-6 FA. Fish oil studies did not always report the oil's concentration of n-3 and n-6 FA in addition to the one of interest. Few studies assessed the effects of EPA alone and only one study assessed the effects of ALA alone. Of most concern was the heterogeneity in the description of the n-3 and n-6 FA contents of infant formulas and the systematic lack of assessment of formula intake (realizing the difficulty of this measurement in human infants). Few trials compared n-3 FA dose, formulation (e.g., ratio of EPA to DHA), or source. No trial compared different n-3 to n-6 FA ratios of supplements or intake. None of the observational studies attempted to determine a threshold effect of any associations between n-3 FA and the outcome of interest. Some observational studies failed to report median or range data of n-3 FA levels within quantiles, confidence intervals (or equivalent) of association hazard ratios, or conducted only linear analyses across a full range of n-3 FA values. In addition, studies varied in the range of n-3 FA status (e.g., intake level) within each study. The applicability of many of the observational studies to the U.S. population may also be limited by the higher baseline intakes of fish and other n-3 FA-containing foods and supplements among the populations in these studies.

For the outcomes related to infant and child development (except for growth patterns), tests used to measure most outcomes were numerous and heterogeneous across studies regardless of the study designs, and follow-up times varied widely. As a result, studies for a number of outcomes of interest could not be pooled, either with studies identified for the original report or with newly identified studies. In addition, the multiplicity of measures all but ensured that some outcome measure would produce a significant effect. Understandably, studies of cognitive, neurological, and visual acuity development with multiple follow-up points were required to use age/stage-appropriate outcome measures, but they seldom attempted to account for these changes in outcome measures.

The RCTs and observational studies differed in a number of ways, making it difficult to compare outcomes across the two study designs. Of note, the doses of n-3 FA supplements in RCTs were often much higher than the highest intake reported for observational studies. Furthermore, not all observational studies explicitly included n-3 FA supplements in their assessment of intake, and almost none of the RCTs attempted to account for background fish or n-3 FA intake as an effect modifier.

Finally, due to the significant heterogeneity across studies, the interpretation of overall meta-analysis results is limited. Only a small number of RCTs conducted dose response assessments (usually with poor results). For those reasons, we did not attempt to do dose-response meta-analysis of observational studies.

Future Research Recommendations

The design of future RCTs should attempt to determine whether particular populations or individuals are more likely to benefit from n-3 FA supplements or fortified formulas, e.g., individuals with relatively low baseline intakes of n-3 FA. Therefore, studies need to measure—and match intervention groups according to—baseline n-3 FA biomarker status (although the current report has not clearly revealed the most relevant biomarkers). Researchers need to reach consensus on standardized formulations and on reporting of concentrations for interventions. The results of this review should help guide these decisions.

Studies also need to ascertain whether n-3 FA are more effective in individuals at increased risk for particular conditions (such as low birth weight, preterm birth, gestational hypertension, or, for infants, risk for delayed visual acuity development or atopy).

Finally, identifying the most promising and clinically relevant outcome measures will be important to expanding the strength of the evidence base for the effectiveness of supplemental n-3 FA for maternal and childhood outcomes. The findings of large cohort studies are still needed to assess the potential role of n-3 FA status in the risk for conditions such as autism spectrum disorder, learning disabilities, and ADHD; however, it may be necessary first to identify clear intermediate risk factors for these conditions, because the length of followup needed for diagnosis of the conditions themselves greatly increases the potential interference of other confounding factors.

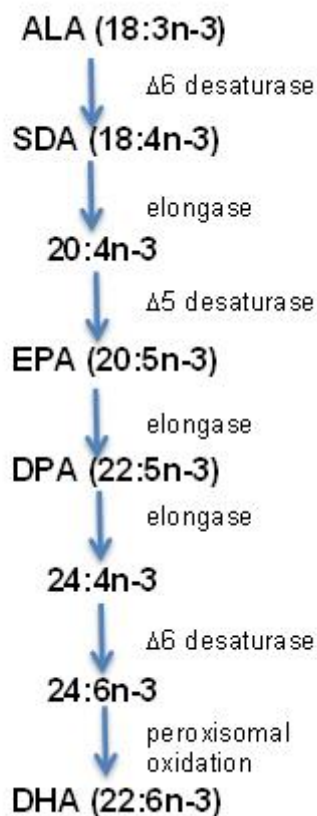
Conclusions

Most studies identified for this report examined the effects of marine oil (or other combinations of DHA and EPA) supplements on pregnant or breastfeeding women or the effects of infant formula fortified with DHA plus arachidonic acid. As with the original report, with the exception of small effects on birth weight and length of gestation, n-3 FA supplementation or fortification seems to have no consistent effects on peripartum maternal or infant health outcomes. Future RCTs need to assess standardized preparations of n-3 and n-6 FA, using a select group of clinically important outcomes, on populations with baseline n-3 FA intakes typical of those of most western populations.

Introduction

The omega-3 fatty acids (n-3 FA) (including alpha-linolenic acid [ALA], stearidonic acid [SDA], eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]) are a group of essential long-chain and very-long-chain polyunsaturated fatty acids (LC-PUFA) that are involved in the eicosanoid pathway and are incorporated into cell membranes. Eicosanoids (including prostaglandins, thromboxanes, and leukotrienes) have wide ranges of physiologic effects and play a key role in inflammation regulation. The metabolic pathway of n-3 FA is shown in Figure 1. ALA is the simplest n-3 FA, from which all other n-3 FA are metabolically derived. ALA must come from the diet, as it cannot be made by the body. ALA is found in plant foods, such as leafy green vegetables, nuts, and vegetable oils such as canola, soy, and flaxseed. SDA can be formed from ALA via $\Delta 6$ -desaturase, the rate-limiting enzyme in the pathway. When SDA enters the metabolic pathway, it is rapidly converted to EPA. EPA can be converted to DPA and vice versa. The rates of conversion from ALA to EPA or DHA are highly variable. Good sources of EPA and DHA in the diet include fin fish, other seafood, other marine sources, and organ meats.

Figure 1. Metabolic pathway of omega-3 fatty acids



A role for n-3 FAs in prenatal and postnatal growth and development and risk for certain chronic diseases has been suggested by a variety of evidence from prospective cohort studies and randomized controlled trials (RCTs). In 2002, the Institute of Medicine (IOM) considered the evidence inadequate to establish an estimated average requirement (EAR) for n-3 FAs.¹ Thus, in

the absence of sufficient evidence, the IOM set only Adequate Intake values (AIs), based on current population intake in the apparent absence of deficiency symptoms.² The IOM set the following AIs for n-3 FA for healthy pregnant women and children:

Pregnant women: 1.4 grams (g)/day (d) of ALA

Infants (≤ 12 months): 0.5 g/d of n-3 FAs

Children (1 to 3 years): 0.7g/d of ALA

Children (4 to 8 years): 0.9 g/d of ALA

In 2004, at the request of the National Institutes of Health's (NIH) Office of Dietary Supplements (ODS), three Evidence-based Practice Centers (EPCs) conducted 11 systematic reviews (SRs) of the evidence for the health effects of n-3 FAs. Included among these SRs was one that encompassed outcomes related to the health of pregnant women and their children.² Maternal outcomes included the risk for pregnancy hypertension and preeclampsia. Child health outcomes included risk for preterm birth, intrauterine growth retardation (IUGR) (small-for-gestational age and low birth weight); birth weight, length, and head circumference; neurological development; visual function in the first year of life; and various indices of cognitive development. Since the original review, many new studies and a number of SRs have examined the role of n -3 FAs in these outcomes. In addition, recent studies have suggested a potential role for n-3s in some related outcomes, e.g., the development of attention and working memory.³

Scope and Key Questions

Scope of the Review

The NIH ODS has a long history of commissioning AHRQ-based systematic reviews and research methodology reports for nutrient-related topics (http://ods.od.nih.gov/Research/Evidence-Based_Review_Program.aspx). The original 2005 systematic review² did not reach strong scientific conclusions for many of the outcomes of interest, most likely related, at least in part, to the fact that some n-3 FA exposures were from fish and other marine sources, some were from dietary supplements, some were indirect (through breast milk), and many studies did not assess biomarkers. In addition, for outcomes of interest for which RCTs were available, observational studies were not considered, whereas for outcomes for which RCTs were unavailable or could not be conducted, the authors relied on observational studies of varying design. Studies of different designs each have their own strengths and weakness that may result in differences in conclusions. For example, observational studies based on self-reported dietary assessments (e.g., food frequency questionnaires) may inaccurately estimate n-3 FA intake; RCTs of specific fish or other n-3 FA-rich food may impose an artificial dietary pattern that might not be applicable to the general population; RCTs of supplements might not fully account for differences in background n-3 FA intake; studies using either study design may have subtle differences in eligibility criteria, e.g., length of follow-up period, or inclusion of ALA, EPA, and DHA or only EPA and DHA, that significantly impacted the final conclusions.

² The use of an AI instead of an EAR indicates the need for more research to determine, with confidence, the mean and distribution of requirements for that nutrient; AIs are based on much less data and more scientific judgment than are EARs.

The current systematic review has four aims: 1) to update the original review on the topic of the effects of n-3 FAs on maternal and child outcomes,² 2) to identify the literature for several additional outcomes of interest (see below) not included in the original review; 3) to include prospective observational studies that were excluded from the original report when two or more RCTs were identified for an outcome of interest; and 4) to use this new review to collect additional information that would enhance the usefulness of this report for policy and clinical applications. Therefore, it is of interest to systematically compare results across different exposure/intervention products and study types (e.g., interventional vs. prospective cohort studies), and to account for differences in background n-3 FA intake.

This update includes the addition of seven new outcomes: (maternal) ante- and postnatal depression, and pediatric attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), learning disabilities, atopic dermatitis, allergies, and respiratory disorders, specifically looking at the risk for (or prevention of) these conditions in otherwise healthy individuals and their offspring, rather than the efficacy of n-3 FA in treating affected individuals. The additional outcomes may present several challenges: a limited literature base; the need to rely largely, if not completely, on population-based cohort studies (RCTs are likely to be rare, and case-control studies are inadequate to address these issues); and the need to assess and distinguish the effects of potential maternal and postnatal exposures on postnatal outcomes. Furthermore, there are ongoing concerns in the scientific community regarding systematic biases and random errors in the determination of n-3 FA intakes from dietary and supplement sources, using currently available assessment tools. The limitations of the current methods have been discussed elsewhere.^{4, 5} To date, no alternate methods are available. Until “error-free” or “bias-free” methodologies are developed, it is crucial to evaluate the available data with the methodological quality and the limitations in mind. Nutrient biomarkers can provide an objective measure of dietary status. However, the correspondence between intake and biomarker concentration reflects not only recent intake but subsequent metabolism (e.g., elongation, desaturation, metabolism to bioactive compounds). Current biomarkers used to estimate n-3 polyunsaturated fatty acids intakes include ALA, EPA, SDA, and DHA, and are measured in adipose tissue, erythrocytes, plasma, or plasma phospholipids, placenta, and umbilical cord.⁶ ⁷Adipose tissue FAs are thought to reflect long-term intake, erythrocytes FAs are thought to reflect the previous 120-day intake, and plasma FAs are thought to reflect more immediate intake.⁷

The 2005 review screened 2,049 abstracts, of which 117 articles (describing 89 studies) were included. Of the 89 studies, 63 were RCTs and 26 were observational studies. This current systematic review updated the outcomes included in the previous review and expanded the scope to include additional maternal (risk for perinatal depression) and childhood (risk for ADHD, autism, learning disabilities, allergy, and respiratory conditions) outcomes. Moreover, the current review systematically evaluated possible reasons for inconsistencies between observational and RCT findings by tabulating causality-related study features such as the Bradford Hill criteria.⁸

Key Questions

The key questions address both issues of efficacy (i.e., causal relationships from trials) as well as associations (i.e., prospective cohort study results and outcomes or risk factors from RCTs for which the randomization may not be applicable). Compared with the key questions from the 2005 report, they expand the scope of the review to include additional maternal and child outcomes, as noted above and described below (shown in bold face).

Key Question 1: Maternal Exposures

- What is the efficacy of maternal interventions involving—or association of maternal exposures to—n-3 FA (EPA, DHA, EPA+DHA [long-chain n-3 FA], DPA, ALA, SDA or total n-3 FA) on the following:
 - duration of gestation in women with or without a history of preterm birth (less than 37 weeks gestation),
 - incidence of preeclampsia/eclampsia/gestational hypertension in women with or without a history of preeclampsia/ eclampsia/ gestational hypertension
 - Incidence of birth of small-for-gestational age human infants
 - **Incidence of ante- and/or postnatal depression in women with or without a history of major depression or postpartum depression**
- What are the associations of maternal biomarkers of n-3 intake during pregnancy and the outcomes identified above?
- What are the effects of potential confounders or interacting factors (such as other nutrients or use of other supplements, or smoking status)?
- How is the efficacy or association of n-3 FA on the outcomes of interest affected by the ratio of different n-3 FAs, as components of dietary supplements or biomarkers?
- How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on the outcomes of interest?
- Is there a threshold or dose-response relationship between n-3 FA exposures and the outcomes of interest or adverse events?
- How does the duration of the intervention or exposure influence the effect of n-3 FA on the outcomes of interest?

Key Question 2: Fetal/childhood exposures

- What is the influence of maternal intakes of n-3 fatty acids or the n-3 fatty acid content of maternal breast milk (with or without knowledge of maternal intake of n-3 FA) or n-3 FA-supplemented infant formula or intakes of n-3 FA from sources other than maternal breast milk or supplemented infant formula on the following outcomes in term or preterm human infants?
 - Growth patterns

- Neurological development
- Visual function
- Cognitive development
- **Autism**
- **Learning disorders**
- **ADHD**
- **Atopic dermatitis**
- **Allergies**
- **Respiratory illness**
- What are the associations of the n-3 FA content or the n-6/n-3 FA ratio of maternal or fetal or child biomarkers with each of the outcomes identified above?

Key Question 3: Maternal or childhood adverse events:

- What are the short and long term risks related to maternal intake of n-3s during pregnancy or breastfeeding on
 - Pregnant women
 - Breastfeeding women
 - Term or preterm human infants at or after birth
- What are the short and long term risks associated with intakes of n-3s by human infants (as maternal breast milk or infant formula supplemented with n-3 FA)?
- Are adverse events associated with specific sources or doses?

Analytic Frameworks

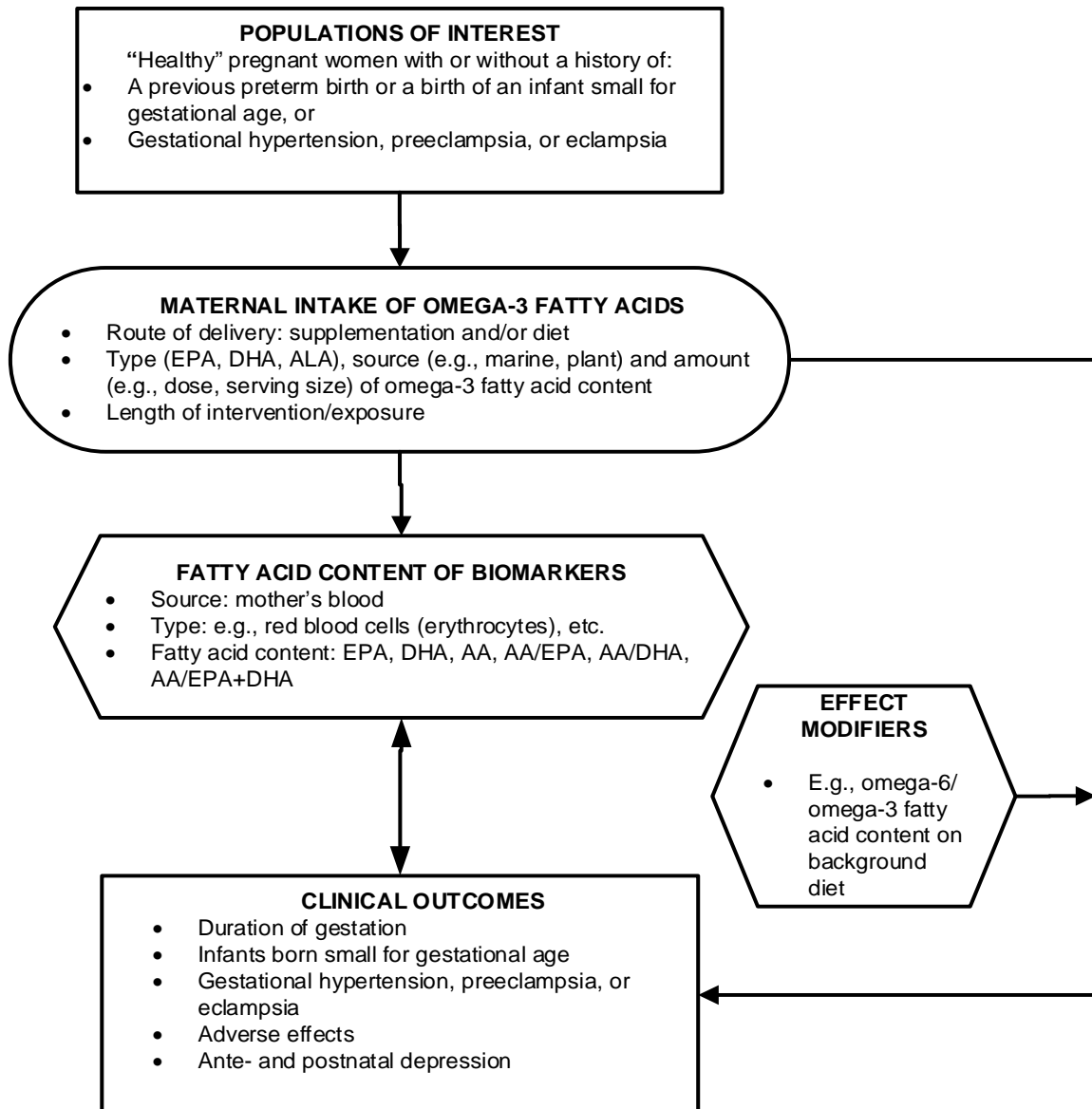
To guide the assessment of studies that examine the association between n-3 FA intake/exposure and the maternal and childhood outcomes of interest, we have created two analytic frameworks that map the specific proposed linkages associating the populations of interest, the exposures, modifying factors, and outcomes of interest. The framework graphically presents the key components of the study questions presented in section II and further described in the Methods section, below.

1. Who are the participants (i.e., what is the population and setting of interest, including the diseases or conditions of interest)?
2. What are the interventions?
3. What are the outcomes of interest (intermediate and health outcomes)?
4. What study designs are of value?

Specifically, this analytic framework depicts the chain of logic that evidence must support to link the intervention (exposure to n-3 FA) to improved health outcomes.

Figure 2. Analytic Framework for n-3 fatty acids in maternal health

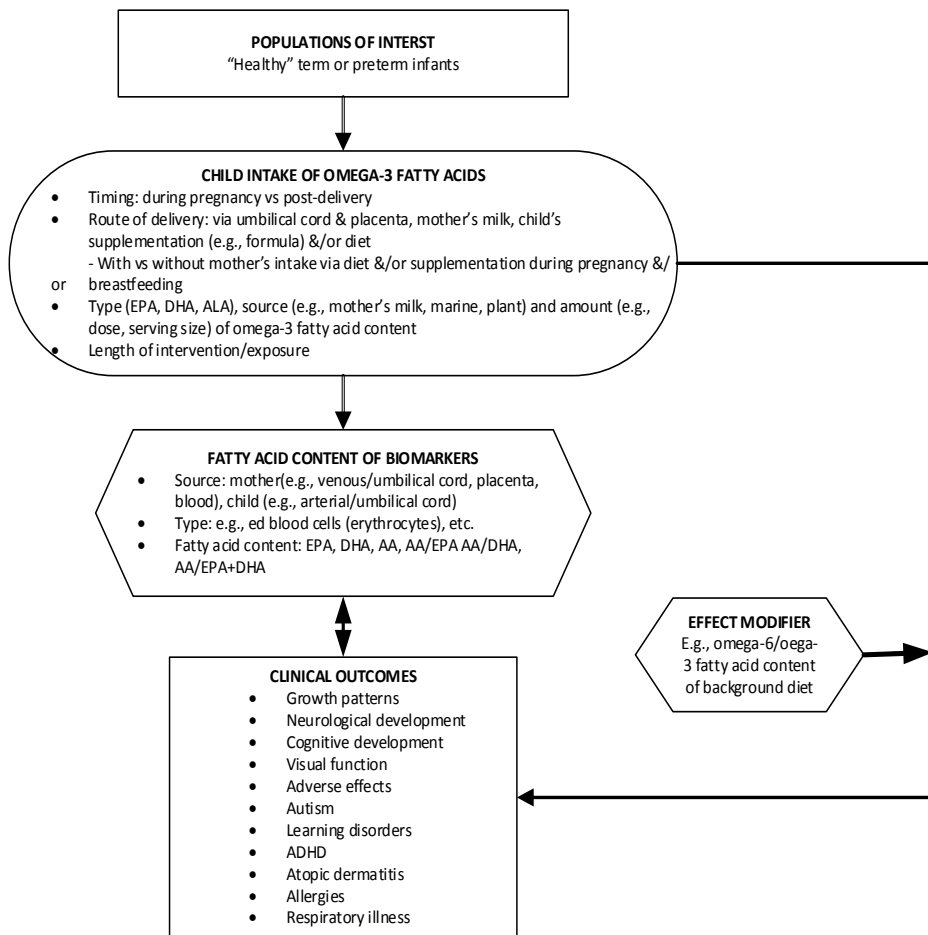
Populations of interest, Exposure, Outcomes, and Effect modifiers are described. Solid connecting arrows indicate associations and effects reviewed in this report.



Legends: This framework concerns the effect of n-3 FA exposure (as a supplement or from food sources) on maternal health outcomes. Populations of interest, Exposure, Outcomes, and Effect modifiers are described. Solid connecting arrows indicate associations and effects reviewed in this report. ALA = alpha-linolenic acid, CAD = coronary artery disease, CHF = congestive heart failure, CKD = nondialysis-dependent chronic kidney disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, SDA = stearidonic acid.

Figure 3. Analytic Framework for n-3 fatty acids in child health

Populations of interest, Exposure Outcomes, Effect modifiers were listed. Solid connecting arrows indicate associations and effects reviewed in this report.



Legends: This framework concerns the effect of n-3 FA exposure (as a supplement or from food sources) on infant health outcomes. Populations of interest, Exposure, Outcomes, and Effect modifiers are described. Solid connecting arrows indicate associations and effects reviewed in this report. ALA = alpha-linolenic acid, CAD = coronary artery disease, CHF = congestive heart failure, CKD = nondialysis-dependent chronic kidney disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, SDA = stearidonic acid.

Methods

The present review evaluates the effects of n-3 FAs (including EPA, DHA, DPA, ALA, SDA, and n-3 biomarkers) on—and the associations between n-3 FA and—maternal and child health outcomes. The Evidence-based Practice Center (EPC) conducted the review of the published scientific literature using established methods as outlined in the Agency for Healthcare Research and Quality (AHRQ)’s Methods Guide for Comparative Effectiveness Reviews.⁹

This review was conducted in parallel with a systematic review of n-3 FA and cardiovascular disease, conducted by another EPC. Several aspects of the reviews are being coordinated, including eligibility criteria regarding interventions and exposures, search strategies, structure of the reviews, and assessments of the studies’ risk of bias, strength of the bodies of evidence, and abstraction of study characteristics needed to assess causality.

Topic Refinement and Review Protocol

We convened a Technical Expert Panel (TEP) to help refine the research questions and protocol. The TEP included international experts in n-3 FA research, academic pediatricians, an obstetrician-gynecologist who represents the American Congress of Obstetricians and Gynecologists, and a pediatrician who represents the American Academy of Pediatrics. Also included in the discussions with the TEP were the ODS Director of and a Senior Scientist and the AHRQ Task Order Officer. We discussed the key questions, analytic framework, study eligibility criteria, literature searches, and analysis plans. In addition, in separate discussions with the ODS representative and our TOO we considered how and whether to assess the concept of causality, particularly for the observational studies. After discussion of the Bradford Hill criteria and related issues regarding causality,⁸ we agreed to provide the study-level data for items that may be pertinent for users of this report to assess causality (this information is included in the Evidence tables in Appendixes C and D).

Furthermore, we had joint discussions with the Brown University EPC—which conducted the parallel report on n-3 FA and cardiovascular disease—and our TOO and the ODS representative to coordinate our protocols and processes. The protocol was entered into the PROSPERO register (registry number CRD42015020638).

Literature search

Search strategy

We modified the existing search strategies from the original report (see Appendix A) to include a complete set of terms for the new outcomes of interest based on searches we have conducted on these topics for previous reviews and consultation with colleagues. We conducted literature searches in Medline (Pubmed), Embase, the Cochrane Collection, Web of Science and CAB. For the topics of depression; ADHD; autism; and cognitive, neurological, and visual function development, we searched PsychInfo. We did not search for unpublished (grey) literature; however a notice was published in the Federal Register requesting unpublished data from manufacturers of omega-3 fatty acid-fortified infant formulae and dietary supplements. Searches for all topics began with the year 2000. For the newly added topics, we “reference mined” articles that we identified to determine whether any studies conducted and published prior to 2000 should be obtained and included. Search results were crosschecked with the list of studies included in the original report (as well as the list of prospective cohort studies excluded

from the original report that must now be included) to ensure that no studies included in the original report are inadvertently included in the current report as “new” studies.

[The search will be updated upon submission of the draft report for peer and public review.]

Appendix A displays the current complete search strategy.

Inclusion and exclusion criteria

The current eligibility criteria are mostly similar to the criteria used in the original 2005 review. The populations are expanded to accommodate the expanded outcomes of interest. The interventions and exposures remain the same as those in the original report, with the addition of two n-3 FA (DPA and SDA). Included study designs have been modified slightly.

The Eligibility Criteria are outlined here according to the PICOT framework, with indications of the key questions to which they apply.

- **Population(s):**
 - Key Question (KQ) 1(Maternal exposures and outcomes)
 - Healthy pregnant women (for outcomes of birth weight, intrauterine growth restriction/small for gestational age, duration of gestation, risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
 - Pregnant women with a history of pre-eclampsia, eclampsia, or pregnancy hypertension (only for outcome of risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
 - Pregnant women with a history of major depressive disorder or postpartum depression (only for the outcome of risk for peripartum depression)
 - Key Question 2 (In utero and postnatal (through the first year of life) exposures and outcomes)
 - Healthy preterm or full term infants of healthy women/mothers whose n-3 fatty acid exposures were monitored during pregnancy
 - Breastfed infants of healthy mothers whose n-3 fatty acid exposure was monitored and/or who participated in an n-3 fatty acid intervention during breastfeeding beginning at birth
 - Healthy preterm or full term infants with and without family history of respiratory conditions (for outcomes related to atopic dermatitis, allergy, respiratory conditions) of mothers whose n-3 exposures were monitored during pregnancy and/or breastfeeding
 - Healthy children or children with a family history of a respiratory disorder, a cognitive or visual development disorder, autism spectrum disorder, ADHD, or learning disabilities, age 0 to 18 years who participated in an n-3 fatty acid-supplemented infant formula intervention or an n-3 supplementation trial during infancy
 - Key Question 3 (Adverse events associated with n-3 interventions)
 - Healthy pregnant women or pregnant women in the other categories described above
 - Offspring of women enrolled in an n-3 fatty acid intervention during pregnancy
 - Offspring of women whose exposure to n 3 fatty acids was assessed during pregnancy

- Children whose exposure to n-3 fatty acids (through breast milk, infant formula, or supplementation) was monitored during the first year of life
- **Interventions/Exposures:**
 - Interventions (KQ1, 2, 3 unless specified):
 - N-3 fatty acid supplements (e.g., EPA, DHA, ALA, singly or in combination;
 - N-3 fatty acid supplemented foods (e.g., eggs) with quantified n-3 content
 - High-dose pharmaceutical grade n-3 fatty acids, e.g., Omacor®, Ropufa®, MaxEPA®, Efamed, Res-Q®, Epagis, Almarin, Coromega, Lovaza®, Vascepa® (icosapent ethyl)
 - Exclude doses of more than 6g/d, except for trials that report adverse events
 - N-3 fatty acid fortified infant formulae (KQ2,3)
 - E.g., Enfamil® Lipil®; Gerber® Good Start DHA & ARA®; Similac® Advance®
 - N-3 fortified follow-up formulae
 - Exclude parenterally administered sources
 - Marine oils, including fish oil, cod liver oil, and menhaden oil with quantified n-3 content
 - Algal or other marine sources of omega-3 fatty acids with quantified n-3 content
 - Exposures (KQ1,2)
 - Dietary n-3 fatty acids from foods if concentrations are quantified in food frequency questionnaires
 - Breast milk n-3 fatty acids (KQ2)
 - Biomarkers (EPA, DHA, ALA, DPA, SDA), including but not limited to the following:
 - Plasma fatty acids
 - Erythrocyte fatty acids
 - Adipocyte fatty acids.
- **Comparators:**
 - Inactive comparators:
 - Placebo (KQ1, 2, 3)
 - Non-fortified infant formula (KQ2)
 - Active comparators
 - Different n-3 sources
 - Different n-3 concentrations (KQ1, 2, 3)
 - Alternative n-3 fortified infant formulae (KQ2)
 - Soy-based infant formula (KQ2)
 - Diet with different level of Vitamin E exposure
- **Outcomes:**
 - Maternal outcomes (KQ1)
 - Blood pressure control
 - Incidence of gestational hypertension

- Maternal blood pressure
 - Incidence of pre-eclampsia, eclampsia
- Peripartum depression
 - Incidence of antepartum depression¹⁰
 - Incidence of postpartum depression, e.g.,
 - Edinburgh Postnatal Depression scale
 - Structured Clinical Interview (SCI)
- Gestational length
 - Duration of gestation
 - Incidence of preterm birth
- Birth weight
 - Mean birth weight
 - Incidence of low birth weight/small for gestational age
- Pediatric Outcomes (KQ2)
 - Neurological/visual/cognitive development
 - Visual development, e.g.,
 - Visual evoked potential acuity
 - Behavioral visual acuity testing
 - Teller's Acuity Card test and others
 - Electroretinography
 - Cognitive development, e.g.,
 - Bayley's mental development index
 - Knobloch, Passamanick, and Sherrard's developmental Screening Inventory scores
 - Fagan Test of Infant Intelligence
 - Stanford-Binet IQ
 - Receptive Vocabulary
 - Peabody Picture Vocabulary Test-Revised
 - Neurological development
 - Electroencephalograms (EEGs) as measure of maturity
 - Psychomotor developmental index from Bayley's scales
 - Neurological/movement impairment assessment
 - Active sleep, quiet sleep, sleep-wake transition, wakefulness
 - Nerve conduction test
 - Latency Auditory evoked potential
 - Risk for ADHD
 - Validated evaluation procedures
 - E.g., Wechsler Intelligence Scale for Children,
 - Behavioral rating scales, e.g., Connors, Vanderbilt, and Barkley scales
 - Risk for Autism spectrum disorders
 - Validated evaluation procedures
 - E.g., Modified Checklist of Autism in Toddlers
 - Risk for learning disabilities
 - Validated evaluation procedures

- Risk for atopic dermatitis
 - Risk for allergies
 - Validated allergy assessment procedures, preferably challenge (skin prick test or validated blood tests accepted)
 - Incidence of respiratory disorders
 - Spirometry in children 5 and over (peak expiratory flow rate [PEFR] and forced expiratory volume in 1 second [FEV₁])
- Key Question 3: Adverse effects of intervention(s)
 - Incidence of specific adverse events reported in trials by study arm
- **Timing:**
 - Duration of intervention or follow-up
 - Key Question 1,3 (maternal interventions/exposures):
 - Interventions implemented anytime during pregnancy but preferably during the first or second trimester
 - Followup duration is anytime during pregnancy (for maternal outcomes of pre/eclampsia or maternal hypertension); term (for outcomes related to birth weight, duration of pregnancy); or within the first 6 months postpartum (for the outcome of postpartum depression)
 - Key Question 2, 3 (infant exposures):
 - Interventions implemented within one month of birth or exposures measured within 1 month of birth
 - Followup duration is 0 to 18 years
- **Settings:**
 - Community-dwelling individuals seen by primary care physicians or obstetricians in private or academic medical practices (KQ1, 3)
 - Community dwelling children seen in outpatient health care or educational settings (KQ2, 3)

We limited the study designs of interest to RCTs, prospective cohort studies, and nested case control studies (cross-sectional, retrospective cohort, and case study designs were excluded; studies must have measure of intake/exposure prior to outcome). Only peer-reviewed studies published in English language were included. Unpublished studies were not included.

To focus on studies of the highest relevance and quality, we also excluded observational studies with enrollment sizes of less than 250 unless no other studies were identified for a particular outcome; we also excluded studies that reported exposures only as servings of fish without calculating n-3 FA intakes, study size, exposure duration, or other similar criteria, if the number of studies identified is very large.

Study selection

The DistillerSR software package was used to manage the search outputs, screening, and data abstraction. Title/abstract screening was conducted in duplicate (after a training session to ensure understanding of the inclusion and exclusion criteria and reasonable inter-rater reliability), using a screening form that lists the inclusion and exclusion criteria and allows selection of reasons for exclusion. All title selections were accepted without reconciliation for further full-text review.

Second-level screening of full text articles was conducted by two reviewers and differences reconciled (the project leaders settle disagreements, if needed).

Abstracts for a subset of ten percent of titles selected from the EMBASE search were reviewed; based on the acceptance rate of the abstracts, it was determined that no additional abstracts for publications identified in the EMBASE search would be screened for inclusion.

Reference lists of existing recent SRs on outcomes of interest were reviewed to ascertain that we did not miss relevant studies.

Data extraction

Accepted studies underwent single abstraction of study-level data and risk-of-bias assessment in Distiller, with audit by an experienced reviewer. Outcome data were abstracted by a biostatistician and audited by an experienced reviewer. We re-extracted data from studies included in the original report that were included in new pooled analyses as needed.

Data collection forms were designed by the project team in Distiller SR, piloted by the reviewers, further modified, and then the final forms piloted with a random selection of included studies to ensure agreement of interpretation. Studies based on large prospective cohorts were identified in their Distiller records to allow comparison to ensure data were not extracted in duplicate. Study-level data included PICOTs, baseline nutritional status/ biomarkers/other evidence of initial exposure to n-3 fatty acids as well as status of other nutrients that could influence outcomes (e.g., vitamin E), method of exposure assessment and associated margin of error, inclusion/exclusion criteria, study design, comorbidities, other potential effect modifiers, analytic methods, and characteristics necessary to assess risk of bias, including recruitment, blinding, allocation concealment, description of completeness of final dataset, funding source, and other potential conflicts of interest.

Outcome data, including clinical outcomes and intermediate outcomes (concentrations of biomarkers), were abstracted in duplicate in Excel files by the biostatistician and one additional reviewer. At the end of the project, abstracted data will be uploaded to the Systematic Review Data Repository (SRDR) for full public accessibility.

Methodological quality (risk of bias) assessment of individual studies

We assessed the methodological quality of each study based on predefined criteria. Risk of bias among RCTs was assessed using the Cochrane Risk of Bias tool,¹¹ which evaluates risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias. Risk of bias among observational studies was assessed using questions relevant for prospective studies from the Newcastle-Ottawa tools.¹² Both tools were supplemented with nutrition-specific items in consultation with the TEP (e.g., those related to uncertainty of dietary assessment measurements and compliance).¹³⁻¹⁵ Studies that reported adverse events were also assessed for adverse event assessment and reporting using the McMaster Quality Assessment Scale of harms (McHarm).¹⁶ Any quality issues pertinent to specific outcomes within a study were noted and considered when determining the overall strength of evidence for conclusions related to those outcomes.

Data Synthesis/Analysis

All included studies were summarized narratively and in summary tables that show the important features of the study populations, design, intervention/exposure, outcomes, and results; we built off and improved on the tables used in the original review. Separate summary tables were used to describe studies that report on a particular outcome of interest.

We analyzed the results of studies of different design separately, combining them if appropriate, and we compared and contrasted populations, exposures, and outcomes across study designs, examining any differences in outcomes between interventional and observational studies.

Statistical data were extracted from all trials with an outcome of interest. We considered meta-analyses when there were at least three trials with similar population (e.g., pregnant women, term infants, preterm infants), intervention (e.g., DHA, DHA+EPA, DHA+AA), follow-up time (e.g. birth, 12 months of age), and outcome measure. For trials that had groups with the same intervention but with varying doses, we averaged the outcome across doses for the main analysis. Forest plots were provided for random effects meta-analysis. We used the Hartung-Knapp-Sidik-Jonkman method for our random effects meta-analysis.¹⁷⁻¹⁹ It has been shown that the error rates from this method are more robust than the previously used DerSimonian and Laird method.²⁰ Heterogeneity was assessed using the I² statistic.²¹ All statistical analyses were performed in R 3.2.0.²²

New trial results were added to original meta-analyses, when appropriate, based on similarity of participants, interventions (including doses), and outcomes.⁹ When sufficient data were available and clinical heterogeneity was minimal, we conducted dose-response meta-analysis (for observational studies) or meta-regression on doses (for RCTs) to support our qualitative synthesis. When new bodies of observational studies were added, possibility for random-effects multivariate dose-response meta-analysis was also assessed.²³⁻²⁷ For meta-analysis of data with clear outliers, sensitivity analysis were conducted, if appropriate to the question.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

The strength of evidence was assessed for each outcome and exposure type using the method outlined in the AHRQ Methods Guide⁹, in which the body of evidence for each outcome is assessed based on the following dimensions: study limitations (risk of bias), reporting bias, consistency (within and across study designs), and precision, as well as the number of studies by study design. Based on these assessments, we assigned a strength-of-evidence rating (i.e., insufficient, low, moderate, or high level of evidence). The data sources, basic study characteristics, and each strength-of-evidence dimensional rating were summarized in “Summary of Evidence Reviewed” tables detailing our reasoning for arriving at the overall strength of evidence rating (Appendix G). Applicability of studies to the populations and interventions that are the focus of the current review was assessed also, as described below.

Assessing Applicability

The primary basis for assessment of applicability was the similarity of average intake of n-3 fatty acids (as fatty fish or other foods) to that of the U.S. and other healthy western populations at baseline. Studies of healthy pregnant women and healthy infants were also judged to have higher applicability than those enrolling women with a prior history of poor pregnancy outcomes

or children with a family history of the conditions of interest. Studies in which the majority of participants were taking n-3 supplements at baseline were also rated as having lower applicability.

Peer Review and Public Commentary

A draft version of this report [is being] reviewed by a panel of expert reviewers, including representatives from [pending] and the general public. The reviewers included experts in [pending]. These experts were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft [will be] made, where appropriate, based on their comments. The draft and final reports are also reviewed by AHRQ. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

This section first describes the results of the literature searches, followed by the key findings, descriptions of the studies that met inclusion criteria, and detailed descriptions of the findings and synthesized outcomes for each of the key questions.

Results of Literature Searches

Our searches identified 3,427 titles/abstracts. An additional search of CAB resulted in 442 titles. Two references were suggested by experts and 22 references were rescreened from the Ottawa report. This yielded 3,893 titles/abstracts that went out for dual screening, of which 3,307 titles/abstracts were excluded for the following reasons: not human (143), not omega-3 (1,507), not in English (1), treatment study that didn't address prevention/risk (184), study design which includes editorials, letters, cross sections study designs, protocols, etc (165), population not of interest (566), omega-3 not orally taken (66), no outcomes of interest (89), does not address the KQ (438), only exposure/intervention was total fish intake (33), study only addressed biomarkers and no other outcomes of interest (2), duplicate data (3), non-systematic review background (75), or no abstract was indexed (35).

We reviewed 586 full text articles, of which 469 were excluded for the following reasons: study was included in the original report (32), participants were not human (3), not omega-3 (49), not in English (1), treatment study only (24), study design (45), population not of interest (32), not oral intake (8), no outcomes of interest (68), did not address a key question (2), fish intake only (13), biomarkers only (38), duplicate data (23), no interventions of interest (4), non-systematic review background (53), systematic review (38), observational studies with less than a sample size of 250 participants (33), articles not found (2), no numerical data (1). A list of references by exclusion reason can be found in Appendix B.

The Federal Register posting did not yield any additional materials to review for possible inclusion.

We include 117 articles in our report. Seventy-four of the articles are randomized controlled trials (RCTs) and 43 are observational studies.

We breakdown the included studies by outcomes which can be found below in the literature flow diagram and in the results chapter of the main report.

Figure 4. Literature flow diagram

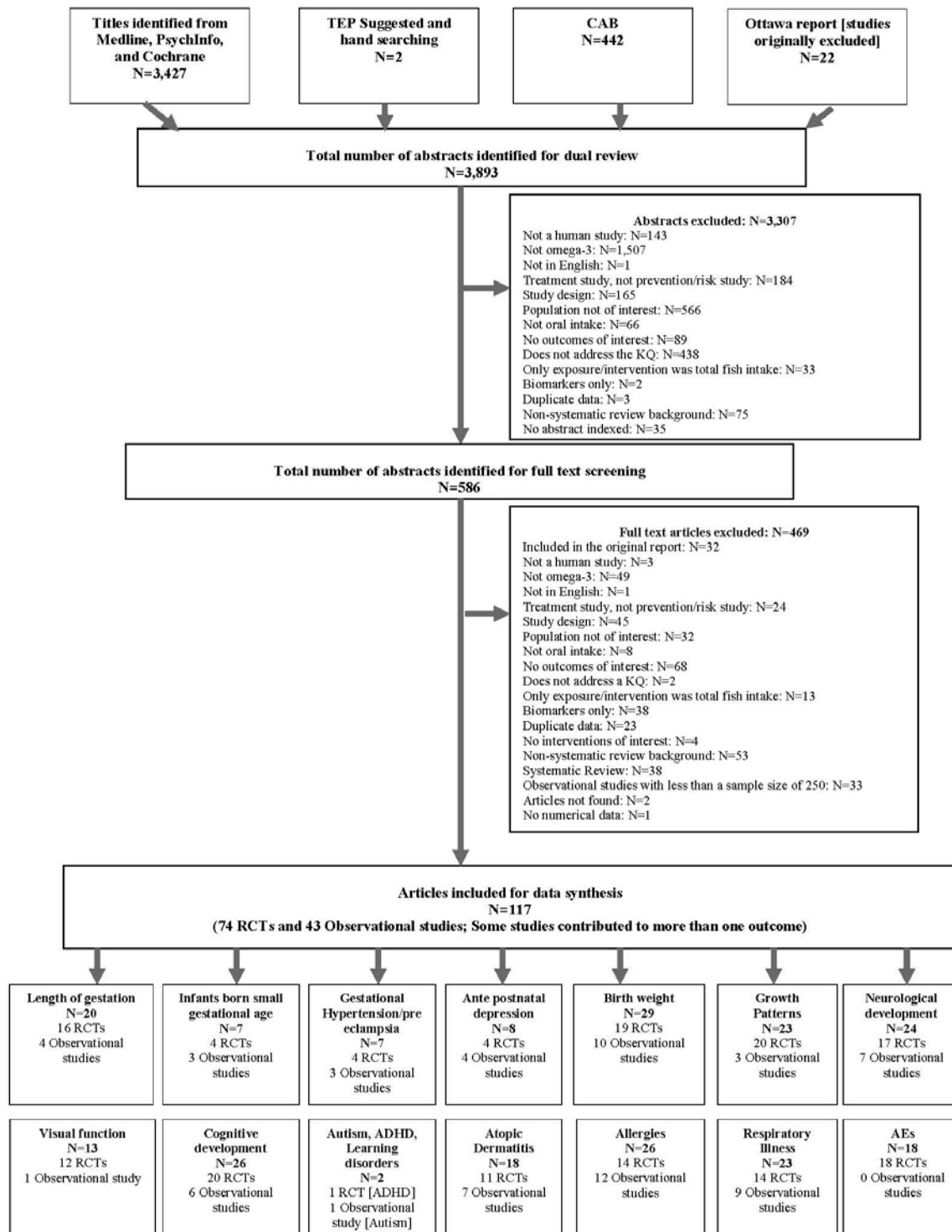


Figure notes: AE(s)=Adverse Event(s); KQ=Key Question; RCT(s)=Randomized Controlled Trial(s); SR(s)=Systematic Review(s)

Findings

Key Question 1: Maternal Exposures

- What is the efficacy of maternal interventions involving—or association of maternal exposures to—n-3 FA (EPA, DHA, EPA+DHA [long-chain n-3 FA], DPA, ALA, SDA or total n-3 FA) on the following:
 - duration of gestation in women with or without a history of preterm birth (less than 37 weeks gestation),
 - incidence of preeclampsia/eclampsia/gestational hypertension in women with or without a history of preeclampsia/eclampsia/gestational hypertension
 - Incidence of birth of small-for-gestational age human infants
 - **Incidence of ante- and/or postnatal depression in women with or without a history of major depression or postpartum depression**
- What are the associations of maternal biomarkers of n-3 intake during pregnancy and the outcomes identified above?
- What are the effects of potential confounders or interacting factors (such as other nutrients or use of other supplements, or smoking status)?
- How is the efficacy or association of n-3 FA on the outcomes of interest affected by the ratio of different n-3 FAs, as components of dietary supplements or biomarkers?
- How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on the outcomes of interest?
- Is there a threshold or dose-response relationship between n-3 FA exposures and the outcomes of interest or adverse events?
- How does the duration of the intervention or exposure influence the effect of n-3 FA on the outcomes of interest?

Length of Gestation (or Gestational Age) and Preterm Birth

Key Findings and Strength of Evidence for Length of Gestation (or Gestational Age) and Preterm Birth

- There is a low level of evidence that maternal supplementation of DHA or DHA-enriched fish oil may increase gestational length, and a low level of evidence that maternal supplementation of EPA+DHA fish oils may not have significant effects on infants' gestational length compared with placebo
 - Pooled analysis of 10 RCTs in healthy pregnant women found a significant increase in gestational age among mother's who received algal DHA or DHA-enriched fish oil supplements (WMD [95% CI]=+0.36 [95% CI 0.01, 0.71] weeks) compared to placebo.
 - Pooled analysis of 5 RCTs showed that maternal fish oil supplementation (EPA+DHA) had no significant effects on gestational age.
 - One RCT in healthy pregnant women found no significant effects of various doses of EPA+DHA supplements on gestational age compared to a ALA-supplemented controls.
- There is a low level of evidence that maternal supplementation of n-3 FA (DHA or EPA+DHA) did not have significant effect on the risk of preterm birth.
 - Pooled analysis of 6 RCTs showed no significant effect of DHA or DHA-enriched fish oil on the incidence of preterm birth
 - Pooled analysis of 9 RCTs (in four publications) found no effects of EPA+DHA supplementation on the incidence of preterm birth.
 - Three prospective observational studies found no associations between maternal n-3 FA intake and either gestational age or risk of preterm birth.
 - One prospective observational study among pregnant women with at least one prior spontaneous preterm delivery found no significant difference in odds of preterm birth when comparing the lowest quartile of maternal erythrocyte n-3 FA biomarker with the upper three quartiles. Only women in quartile 2 of erythrocyte n-3 FA levels had a significantly lower odds of preterm birth compared to those in quartile 1.

Description of Included Studies

The original report included 15 RCTs (in 10 publications – one publication by Olsen et al.²⁸ was a pooled data of six different RCTs) investigating maternal intake of n-3 FA supplementation on infants' gestational age (GA). Of these, eleven RCTs compared fish oil capsules (EPA+DHA doses ranged from 0.1 to 5 g/d) with placebo (olive oil and coconut oil), two compared high-DHA eggs (DHA 133-184 mg/d) with regular-DHA eggs (DHA 33-35 mg/d), one compared DHA-rich cod liver oil (1183 mg/d DHA; 803 mg/d EPA; 27.5 mg/d AA) with corn oil (8.3 mg/d DHA), and one compared margarine containing different amount of ALA and LA (ALA group: 2.82 g/d ALA and 9.02 g/d LA; control group: 0.03 g/d ALA and 10.94 g/d LA). Ten of the 15 RCTs did not find a significant effect of maternal n-3 FA supplementation on infants' in gestational age. The other five of RCTs reported a significant increase in infants' gestational comparing maternal n-3 FA supplementation (1 study of high-DHA eggs with 133 mg/d DHA and 4 of fish oil supplementation with EPA+DHA ranging from 2.2. to 5 g/d). Ten of these 15 RCTs also reported incidence of premature delivery outcome. N-3 FA supplementation did not have significant effects on the proportion of premature deliveries in these studies.

Random-effects meta-analyses of 8 RCTs (in three publications - one publication by Olsen et al.²⁸ was a pooled data of six different RCTs) comparing maternal fish oil supplementation (EPA+DHA) to placebo showed that the odds of premature deliveries did not differ significantly between groups (OR 0.88; 95% CI 0.62, 1.25). Similarly, meta-analysis of two RCTs comparing maternal intake of high-DHA eggs with regular-DHA eggs showed that the odds of premature deliveries did not differ significantly between groups (OR 0.53; 95% CI 0.13, 2.29).

The original report only included 1 prospective cohort study. This cohort study reported a positive association between plasma triglyceride AA content and gestation length. However, the study did not find a significant association between maternal plasma triglyceride n-3 FA and the length of gestation.

Fourteen new RCTs and three observational studies were identified for the current report. All studies were conducted among healthy, pregnant women and followed up until birth. Overall we found a low level of evidence that maternal supplementation of DHA or DHA-rich fish oils may increase gestation length but the minimal DHA dose threshold for the effect is still unclear. However, there is a low level of evidence that that maternal supplementation of EPA+DHA fish oils may not have significant effect on infants' gestational length compared with placebo. Furthermore, there is a low level of evidence that maternal supplementation of n-3 FA did not have significant effect on the risk of preterm birth. Limited evidence from one RCT and one cohort study suggested that effects of n-3 FA on gestation length and risk of preterm birth may be larger in women with history of spontaneous preterm deliveries.

Randomized Controlled Trials

Fourteen unique RCTs were identified for the current report. Of these, three RCTs (in 5 publications) compared algal DHA supplements with placebo,²⁹⁻³³ eight compared DHA-rich fish oil supplementation (DHA:EPA ratio $\geq 5:1$) with controls,³⁴⁻⁴¹ and three compared fish oil (EPA+DHA, DHA:EPA ratio $< 5:1$) with placebo,⁴¹⁻⁴³ and one compared five different doses of fish oil supplementation (EPA+DHA 0.1, 0.3, 0.7, 1.4 and 2.8 g/d) with ALA control (ALA 2.2 g/d).⁴⁴ Of these, one RCT compared both DHA-rich fish oil supplement and fish oil supplement, with placebo.⁴¹

All 14 RCTs reported gestation length outcome. Among these, five RCTs (in 7 publications) also reported the incidence of preterm birth outcome.^{30-34, 36, 43}

DHA

Three RCTs (in 5 publications) randomized healthy pregnant women between 8 and 22 weeks of gestation to algae-oil source of DHA supplements (0.2 to 0.6 g/d DHA) or placebo (soybean, corn, or olive oil).²⁹⁻³³ Of these, two RCTs reported gestation length outcome in a total of 302 mothers and their infants living in the U.S.³⁰ and 973 mothers and their infants in Mexico (POSGRAD trial),³¹⁻³³ and one RCT reported the outcome of preterm-premature rupture of membranes in a total of 253 pregnant women in Italy.²⁹ It should be noted that, of the three publications from POSGRAD trial, Ramakrishnan et al. (2010) publication analyzed the largest number of study participants,³¹ while the other two publications analyzed a subset of the trial participants.^{32, 33} Thus, only results from Ramakrishnan et al. (2010) was included in our meta-analysis. The two RCTs that reported gestation length outcome both found no significant effect of DHA (0.4 and 0.6 g/d) supplementation on the length of gestation compared with placebo. Furthermore, these two RCTs also showed no significant difference in the incidence of preterm birth between groups.³⁰⁻³³ The third RCT found a reduced incidence of membrane rupture (0.8%

vs. 3.2%, $P=0.02$) and a longer duration of gestation (data not reported) in the DHA supplementation group ($n=129$) than in the placebo group ($n=126$)

Eight RCTs randomized healthy pregnant women between 12 and 24 weeks of gestation to DHA-rich fish oil supplementation or controls.³⁴⁻⁴¹ Studies were conducted in the U.S. ($n=4$), Germany ($n=2$), Australia ($n=1$), and Netherlands ($n=1$). Of the eight RCTs, three compared DHA cereal-based bars (mean DHA 214-240 and EPA 27-30 mg/d; DHA:EPA ratio = 8) with placebo bars,³⁷⁻³⁹ four compared DHA-rich fish oil supplements (DHA 200-1020 and EPA 100-180 mg/d; DHA:EPA ratio = 5-8),^{36, 40, 41} with controls (vegetable oil, nutritional counseling, vitamins and minerals, or soy oil), and one is a three-arm RCT compared DHA-rich fish oil plus soybean oil (DHA 220 and EPA 36 mg/d plus ALA 32 mg/d), DHA-rich fish oil plus AA (DHA 220 and EPA 36 mg/d plus AA 220 mg/d) with placebo (soybean oil).³⁵ Four of the eight RCTs with lower DHA doses (0.2-0.22 g/d) did not find significant difference in the mean gestational age between DHA supplementation and placebo in a total of 290 infants,^{35, 37, 39, 40} but one found an increase in gestational age (+0.9 [95% CI 0.24, 1.56] weeks) compared DHA cereal-based bars (mean DHA 214-240 and EPA 27-30 mg/d, $n=14$) with placebo bars ($n=15$).³⁸ The other three RCTs with higher DHA doses (0.8-1.02 g/d) all found a significant higher mean gestational age in infants whose mothers received DHA-rich fish oil supplement compared with those whose mothers received placebo (+0.14 to +1.3 weeks) in a total of 2656 infants.^{34, 36, 41} On the other hand, two of these three RCTs with higher DHA doses (0.8 and 1.02 g/d) both did not find significant difference in the incidence of preterm birth between groups (OR 0.75 [95% CI 0.54, 1.04] and OR 0.78 [95% CI 0.17, 3.56]).^{34, 36}

Ten RCTs showed that the mean gestational age was significantly higher in infants whose mothers received algal DHA or DHA-rich fish oil supplement compared with those whose mothers received placebo (WMD [95% CI] 0.36 [0.01, 0.71] grams), with large heterogeneity ($I^2 = 77.7$). (Figure 5) However, our update random-effect meta-analysis of six RCTs (two from the original report) found no significant effects of DHA or DHA-rich fish oil supplement on the incidence of preterm birth compared with placebo (OR [95% CI 0.88 [0.63, 1.23]], with small heterogeneity ($I^2 = 8.8$). (Figure 6)

Figure 5. Length of gestation (weeks) – DHA vs. placebo

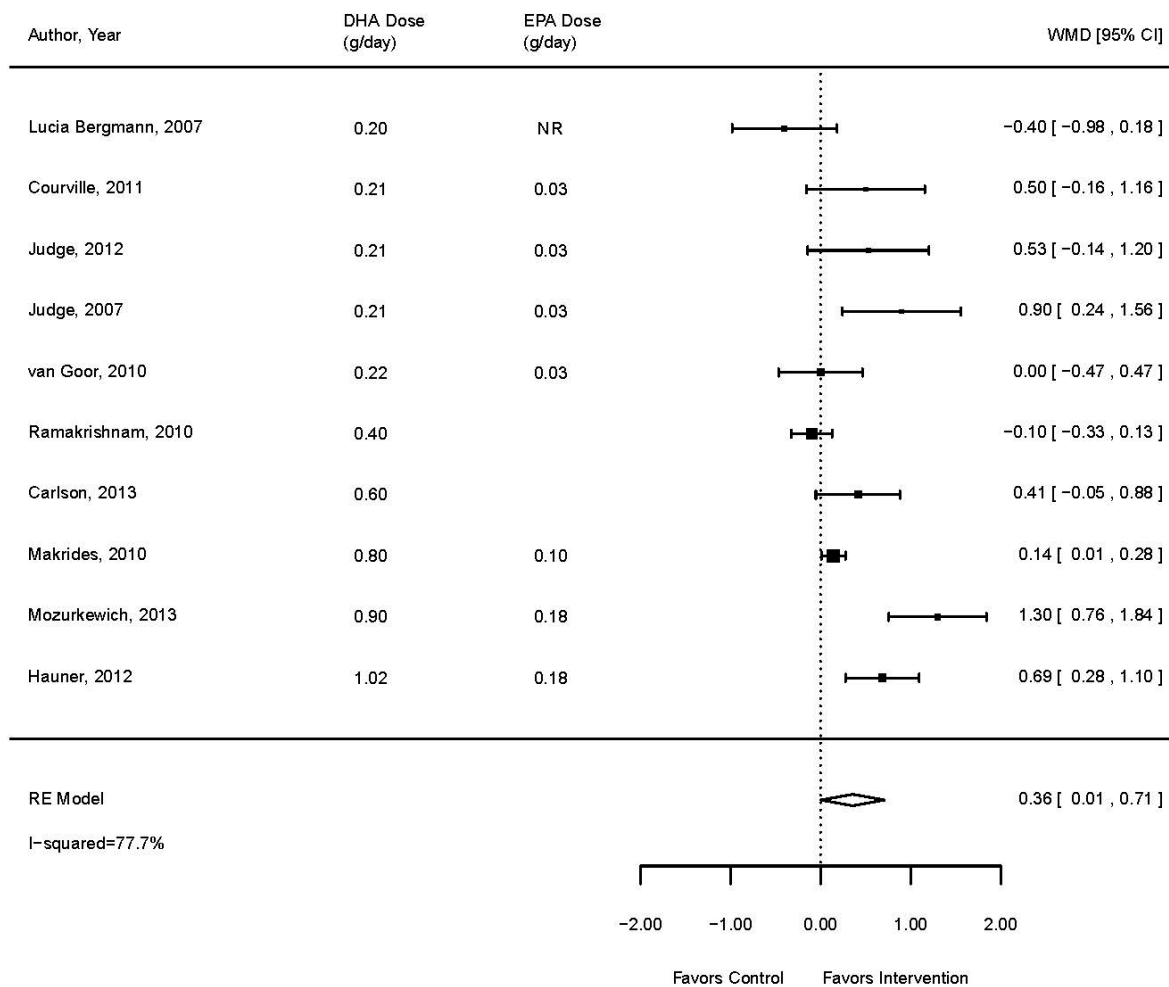
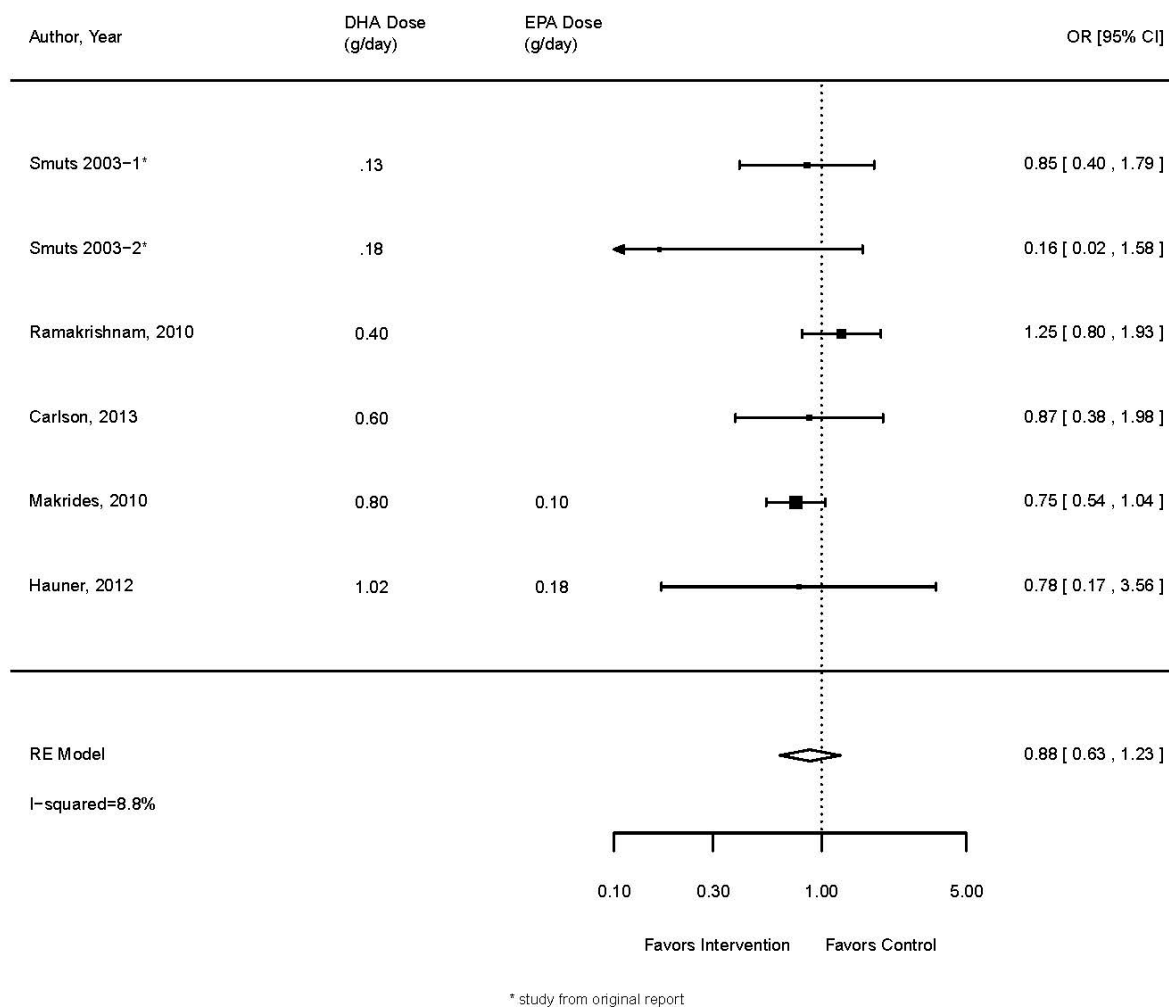


Figure 6. Incidence of premature birth – DHA vs. placebo



EPA+DHA

Three RCTs randomized healthy pregnant women between 12 and 22 weeks of gestation to fish oil supplements (EPA+DHA) or placebo (soybean oil, corn oil, olive oil or inert mineral oil).⁴¹⁻⁴³ Studies were conducted in the U.S. (n=2) and Australia (n=1). The doses of EPA ranged from 1.06 to 1.20 g/d, and the doses of DHA ranged from 0.27 to 2.2 g/d. The DHA to EPA ratio ranged from 0.25 to 2. The total doses of EPA plus DHA ranged from 1.3 to 3.3 g/d. Two of the three studies did not find a significant effect of maternal fish oil supplementation (EPA+DHA 1.33 and 3.3 g/d) on infants' gestational age compared with placebo) in a total of 152 healthy pregnant women,^{41, 42} while the third study found that maternal fish oil supplementation (EPA+DHA 2 g/d) significantly increased the infants' mean gestational age (+0.30 [95% CI 0.07, 0.53] weeks, n=852) compared with placebo.⁴³ However, there was no significant

difference in the incidence or preterm birth between groups in this study (OR 0.85 [95% CI 0.65, 1.12]). It should be noted that this study is the only RCT (out of the 14 RCTs reported gestation length outcome) enrolled healthy pregnant women with a history of at least one prior singleton preterm delivery.⁴³

Three RCTs showed that maternal fish oil supplementation (EPA+DHA doses ranged from 1.3 to 3.3 g/d) did not have significant effect on infants' gestational age compared with placebo (WMD [95% CI] 0.26 [0.00, 0.53]), with no heterogeneity ($I^2 = 0\%$). (Figure 7) The update random-effect meta-analysis of nine RCTs (in four publications - one publication by Olsen et al.²⁸ was a pooled data of six different RCTs) found no significant effects of fish oil supplement on the incidence of preterm birth compared with placebo (OR [95% CI] 0.86 [0.65, 1.15]), with no heterogeneity ($I^2 = 0$). (Figure 8)

Figure 7. Length of gestation (weeks) – DHA + EPA or fish oil vs. placebo

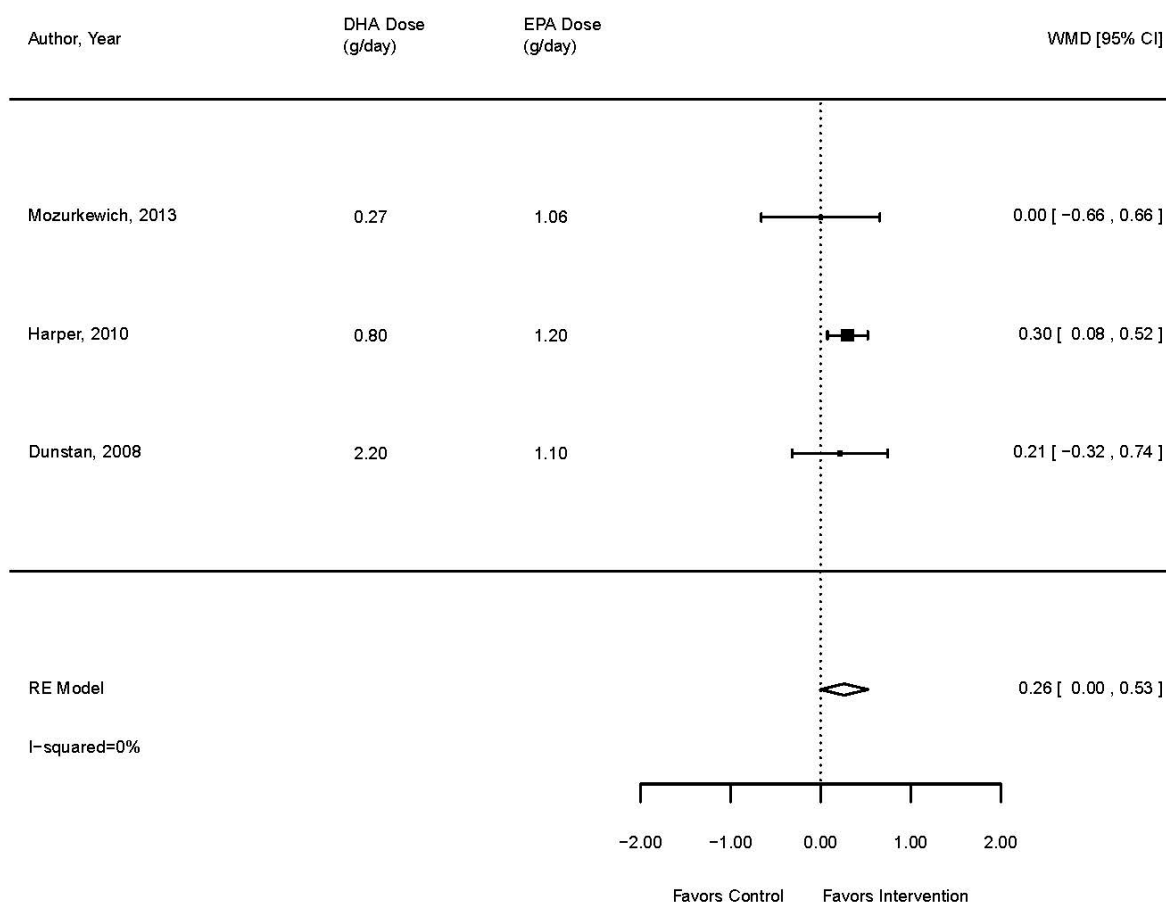
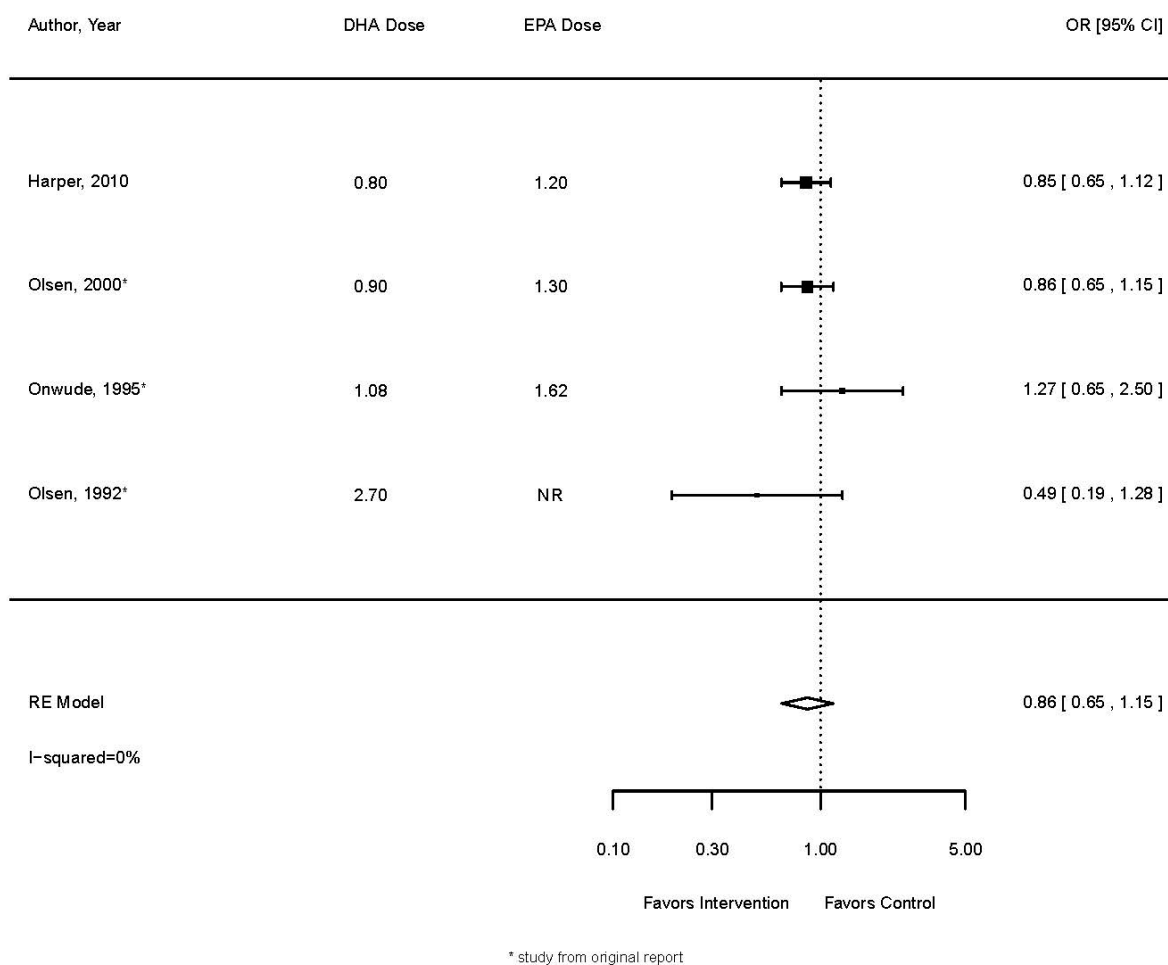


Figure 8. Incidence of premature birth – DHA + EPA or fish oil vs. placebo



EPA+DHA vs. ALA

One RCT compared five different doses of fish oil supplementation (EPA+DHA 0.1, 0.3, 0.7, 1.4 and 2.8 g/d) with ALA control (ALA 2.2 g/d) from week 17–27 of gestation until delivery in a total of 3098 healthy pregnant women with low dietary intake of fish (lowest 20% of fish consumption).⁴⁴ There were no significant differences in gestation length between any of the fish oil supplementation groups and the control group. Specifically, the mean differences in gestational length ranged from -0.7 to +0.3 days between fish oil and ALA control groups.

Observational studies

Three prospective cohort studies were identified for the current report. Of these, two studies assessed the associations between maternal dietary intake of n-3 FA (from foods or supplements)

and infants' gestational age.^{45, 46} One of the two studies also analyzed the relationship between maternal dietary intake of n-3 FA and risk of preterm birth.⁴⁵ The third study examined the relationships between maternal n-3 FA biomarkers and infants' gestational age.⁴⁷

n-3 FA Intake

Two studies assessed the associations between maternal n-3 FA intake from supplements and infants' gestational ages.^{45, 46} Oken et al. (2004)⁴⁵ evaluated the association between quartiles of maternal DHA+EPA intake median 0.27 to 0.38 g/d at first trimester (median EPA+DHA from 0.02 to 0.36 g/d, n= 1797), second trimester (median EPA+DHA from 0.02 to 0.38 g/d, n=1663), and third trimesters (median EPA+DHA from 0.05 to 0.27 g/d, n=2070) trimesters and gestational ages. No significant associations were found. This study also compared the risk of preterm birth between the highest and lowest quartiles of maternal DHA+EPA intake, and there was no significant association was found (OR 1.1 [95% CI 0.7, 1.9].⁴⁵ Badart-Smook et al. (1997)⁴⁶ reported that "No significant correlations were observed between any of the nutrients [including sum of n-3 FA+AA] and birth weight or the length of gestation" (data not shown) in 372 healthy pregnant women of 22th gestation.

n-3 FA Biomarkers

One study examined the relationships between maternal erythrocyte DHA+EPA biomarkers and risk of preterm birth (<37 weeks of GA) in 852 pregnant women with at least one prior spontaneous preterm delivery.⁴⁷ The study showed that the adjusted odds ratio for preterm birth among women in the lowest quartile compared with women in the 3 highest quartiles combined was 1.41 (0.97 – 2.05). When the top 3 quartiles were compared to the lowest quartile (erythrocyte DHA+EPA <3.052 % of total FA), only women in quartile 2 (erythrocyte DHA+EPA 3.052-3.719 % of total FA), but not quartiles 3 (erythrocyte DHA+EPA 3.723-4.426 % of total FA) and quartile 4 (erythrocyte DHA+EPA >4.426 % of total FA), had a statistically significant reduction in the odds of preterm birth compared with those in quartile 1 (adjusted OR 0.59 [95% CI 0.37, 0.94]).

Table 1. RCTs for Length of Gestation (or Gestational Age) and Preterm Birth

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Makrides et al., 2010³⁴</p> <p>Study name: DOMInO</p> <p>Study dates: 2005-2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up article(s) ^{48, 49, 50, 51, 52, 53, 3}</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 2399 Pregnant withdrawals 1</p> <p>Infants enrolled 605 Infants withdrawals 32 Infants completers 726</p> <p>Pregnant age: 28.9 (DHA5.7; control5.6)</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: with singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments</p> <p>Exclusion Criteria: already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home</p>	<p>Start time: Pregnant < 21 week's gestation</p> <p>Duration: NR</p> <p>Arm 1: vegetable oil capsules Description a blend of 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Manufacturer Efamol, Surrey, England. Dose 3* 500mg capsule / day Blinding All capsules were similar in size, shape, and color Arm 2: DHA Description DHA-rich fish oil concentrate Manufacturer ; Incromega 500 TG, Croda Chemicals, East Yorkshire, England Dose 500mg capsule *3/day DHA 800mg EPA 100mg</p>	<p>Outcome gestational age Follow-up time birth Arm 1 Sample size 1202 median 281 IQR (275, 287) Arm 2 Sample size 1197 median 282 IQR (275, 288) Outcome incidence of premature birth Follow-up time birth Arm 1 88/1202 (7.34%) Arm 2 67/1197 (5.6%)</p>
<p>Knudsen et al., 2006⁴⁴</p> <p>Study name: Danish National Birth Cohort</p> <p>Study dates: 2001-</p> <p>Study design: Trial randomized parallel</p> <p>Location: Denmark</p> <p>Funding source / conflict: NR</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 3098 Pregnant withdrawals 1033 Pregnant completers 2065</p> <p>Pregnant age: Group 01: 28.4 years Group 03: 28.7 years Group 07: 28.4 years Group 14: 28.9 years Group 28: 28.8 years</p>	<p>Inclusion Criteria: Low dietary intake of fish (lowest 20% of fish consumption), no use of fish oil capsules in pregnancy, gestational age 17-27 weeks.</p> <p>Exclusion Criteria: NR</p>	<p>Start time: Pregnant 17-27 weeks gestation</p> <p>Duration: Pregnant until delivery</p> <p>Arm 1: CG Description control group (flax oi) N-3 Composition. Blinding The women in the control group were allocated to any treatment and were not contacted at all. ALA 2.2 g/d Arm 2: 01 Description Treatment Group 1 Brand name Futura Fish Oil</p>	<p>Outcome gestational age Follow-up time birth Arm 1 Sample size 748 mean 280.6 SD (11.7) Arm 2 Sample size 229 mean 281.5 SD (12.6) Arm 3 Sample size 224 mean 279.7 SD (12) Arm 4 Sample size 222 mean 280.5 SD (12.6) Arm 5 Sample size 212 mean 280.6 SD (12.6) Arm 6 Sample size 187 mean 279.6 SD (14.8)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Follow-up article(s) ⁵⁴ , ⁵⁵	<p>Group C18: 28.8 years Group CG: 28.5 years</p> <p>Race of Mother: NR</p>		<p>Manufacturer Dansk Droge A/S, Ishoej, Denmark Active ingredients 13.4 mg D-alpha-tocopherol per gram N-3 Composition 32% EPA, 22% DHA Dose 1 0.5 g three times per week Total N-3 0.1 g per day Arm 3: 03 Description Treatment group 2 Brand name Futura Fish Oil Manufacturer Dansk Droge A/S, Ishoej, Denmark Active ingredients 13.4 mg D- alpha-tocopherol per gram Dose 1 0.5 g capsule per day Total N-3 0.3 g per day Arm 4: 07 Description Treatment group 3 Brand name Futura Fish Oil Manufacturer Dansk Droge A/S, Ishoej, Denmark Active ingredients 13.4 mg D- alpha-tocopherol per gram N-3 Composition 32% EPA, 22% DHA Dose 1 1 g capsule per day Total N-3 0.7 g per day Arm 5: 14 Description Treatment group 4 Brand name Futura Fish Oil Manufacturer Dansk Droge A/S, Ishoej, Denmark Active ingredients 13.4 mg D- alpha-tocopherol per gram N-3 Composition 32% EPA, 22% DHA Dose 2 1g capsules per day Total N-3 1.4 g per day Arm 6: 28 Description Treatment group 5 Brand name Futura Fish Oil Manufacturer Dansk Droge A/S, Ishoej, Denmark Active ingredients 13.4 mg D-alpha-tocopherol per gram N-3 Composition 32% EPA, 22% DHA Dose 4 g per day Total N-3 2.8g per day Arm 7: c18 Description Treatment group 6 - flax oil Brand name Prima FlaxTM Manufacturer Bioriginal Food & Science Corp.,</p>	Arm 7 Sample size 176 mean 280.7 SD (12.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Saskatoon, Canada Dose 4 1-g capsules of flax oil ALA 2.2g per day	
Dunstan et al., 2008 ⁴² Study name: Dunstan Study dates: 2000-2003 Study design: Trial randomized parallel Location: Australia Funding source / conflict: NR Follow-up article(s) ^{56, 57, 58, 59} ,	Study Population: Healthy infants Pregnant women with allergies Pregnant enrolled 98 Pregnant completers 83 Infants enrolled 83 Infants withdrawals 11 (7 FO, 4 control) Infants completers 72 Pregnant age: Fish oil: 30.9 Control: 32.6 (Fish oil: 3.7 Control: 3.6) Infant age: Term (mean gestational period 275 days) Race of Mother: NR (NR)	Inclusion Criteria: Healthy term infants of pregnant women enrolled in RCT of gestational supplementation Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected	Start time: Pregnant 20 weeks gestation Duration: Pregnant to term Arm 1: Control Description olive oil placebo Blinding capsules image matched Maternal conditions Current smoker 0% Maternal allergies 100% Arm 2: Fish oil Description same Manufacturer Ocean Nutrition, Halifax Nova Scotia Active ingredients 3-4mg/g vitamin E Viability none reported Dose 4 1-gm capsules fish oil per day Maternal conditions DHA 2.2 EPA 1.1 Current smoker 0% Maternal allergies 100% Other comment 1 fish oil supplying 2,2g/d DHA and 1.1g/day EPA	Outcome gestational age Follow-up time birth Arm 1 Sample size 39 mean 274.5 SD (8) Arm 2 Sample size 33 mean 276 SD (8)
van Goor et al., 2010 ³⁵ Study name: Groningen LCPUFA study Study dates: enrollment from December 2004 until December 2006 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict:	Study Population: Healthy pregnant women Breast-feeding women Pregnant enrolled 183 Pregnant completers 125 Infants completers 119 Pregnant age: 32 years (5 years) Infant age: 14 to 20 weeks gestation	Inclusion Criteria: healthy women with a first or second low-risk singleton pregnancy Exclusion Criteria: women with vegetarian or vegan diets and women with diabetes mellitus	Start time: Pregnant 14 to 20 weeks gestation Infants 14 to 20 weeks gestation Duration: Pregnant until 3 months after delivery Infants until 3 months of age Arm 1: placebo Description soybean oil capsule Manufacturer Wuhan Alking Bioengineering Active ingredients standard dose vitamins and minerals N-3 Composition. Dose 2 capsules Maternal conditions ALA 60 mg	Outcome gestational age birth Follow-up time birth Arm 1 Sample size 36 mean 40.2 SD (1) Arm 2 Sample size 42 mean 40.2 SD (1.1) Arm 3 Sample size 41 mean 40.2 SD (1.1)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Industry, Government Follow-up: 12 weeks ⁶⁰ Follow-up article(s) ^{61, 62, 63, 64, 65, 66, 67, 68}	Race of Mother: NR (100)		DHA 0 EPA 0 AA 0 Other dose 1 LA 535 mg Current smoker 2% Arm 2: DHA group Description DHA fish oil capsule Manufacturer Wuhan Alking Bioengineering Active ingredients standard dose vitamins and minerals Dose 2 capsules Maternal conditions ALA 32 mg DHA 220 mg EPA 34 mg AA 15 mg Current smoker 2% Other comment 2 LA 274 mg Arm 3: DHA + AA group Description DHA + AA capsule Brand name Marinol D40 Manufacturer Lipid Nutrition B.V., Wormerveer, The Netherlands Active ingredients standard dose vitamins and minerals Dose 2 capsules Maternal conditions ALA 7 mg DHA 220 mg EPA 36 mg AA 220 mg Other dose 2 LA 46 mg Current smoker 3%	
Hauner et al., 2012 ³⁶ Study name: INFAT Study dates: july 14 2006 - may 22 2009 Study design: Trial randomized parallel Location: Germany	Study Population: Healthy pregnant women Pregnant enrolled 208 Pregnant withdrawals 38 Pregnant completers 170 Infants enrolled 188 Infants withdrawals 18 Infants completers 170	Inclusion Criteria: healthy pregnant women before the 15th wk of gestation, between 18 and 43 y of age, prepregnancy BMI (in kg/m2) between 18 and 30, willingness to implement the dietary recommendations, sufficient German language skills.	Start time: Pregnant 15th wk of gestation Duration: Pregnant to 4 mo postpartum Arm 1: Control Description brief semistructured counseling on a healthy balanced diet according to the guidelines of the German Nutrition Society and were explicitly asked to refrain from taking fish oil or DHA supplements N-3 Composition.	Outcome gestational age Follow-up time birth Arm 1 Sample size 96 mean 275.1 SD (11.4) Arm 2 Sample size 92 mean 279.9 SD (8.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Funding source / conflict: Industry, Government</p> <p>Follow-up article(s) ^{69, 70, 71}</p>	<p>Pregnant age: 31.9 (4.9) 18-43</p> <p>Race of Mother: NR (NR)</p>	<p>Exclusion Criteria: high-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity .4); hypertension; chronic diseases (eg, diabetes) or gastrointestinal disorders accompanied by maldigestion, malabsorption, or elevated energy and nutritional requirements (e.g., gluten enteropathy); known metabolic defects (eg, phenylketonuria); psychiatric diseases; hyperemesis gravidarum; supplementation with n-3 LCPUFAs before randomization; and alcohol abuse and smoking.</p>	<p>N-6 N-3 2.80 +- 1.17 (SD) at 32nd wk of gestation AA 10.15 +- 3.89 SD) at 32nd wk of gestation Arm 2: Intervention Description Fish-oil supplement + nutritional counseling (to normalize the consumption of AA Brand name Marinol D-40 Manufacturer Lipid Nutrition DHA 1020 mg EPA 180 mg N-6 N-3 1.54 +- 0.63 (SD) at 32nd wk of gestation AA 8.82 +- 2.84 (SD) at 32nd wk of gestation Other comment 1 Vit E 9 mg</p>	
<p>Carlson et al., 2013³⁰</p> <p>Study name: NR</p> <p>Study dates: 2006.01-2011.10</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 350 Pregnant withdrawals 49 Pregnant completers 301</p> <p>Pregnant age: placebo: 24.8; DHA: 25.3 (placebo 4.7; DHA 4.9)</p> <p>Race of Mother: Black (46%;37%) Non-black (54%; 63%)</p>	<p>Inclusion Criteria: Englishspeaking, between 8 and 20 wk of gestation, between 16 and 35.99 y of age, and planning to deliver at a hospital in the Kansas City metropolitan area</p> <p>Exclusion Criteria: carrying more than one fetus, had preexisting diabetes mellitus or systolic blood pressure \$140 mm Hg at enrollment, or had any serious health condition likely to affect the prenatal or postnatal</p>	<p>Start time: Pregnant 99.6/102.9 day</p> <p>Duration: Pregnant enrollment to birth</p> <p>Arm 1: Placebo Description half soybean and half coin oil (Manufacturer DSM Nutritional Products) Active ingredients a-linolenic acid Dose 3 *capsule 200/day Blinding both DHA and placebo capsules were orange flavored Arm 2: DHA Description marine algae-oil source of DHA (Manufacturer DHASCO; DSM Nutritional Products, formerly Martek Biosciences) Dose 200 mg capsule, 3 times a day DHA 200mg/capsule * 3</p>	<p>Outcome gestational age Follow-up time birth Arm 1 Sample size 147 mean 272.8 SD (17) Arm 2 Sample size 154 mean 275.7 SD (11.2) Outcome incidence of premature birth Follow-up time birth Arm 1 13/147 (8.8%) Arm 2 12/154 (7.8%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		growth and development of their offspring, including cancer, lupus, hepatitis, HIV/AIDS, or a diagnosed alcohol or chemical dependency. or if the initial screening based on their self-reported weight and height suggested a BMI (in kg/m2 >=40).		
<p>Courville et al., 2011³⁷</p> <p>Study name: NR</p> <p>Study dates: nr</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry, Government</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 47 Pregnant withdrawals 0 Pregnant completers 47</p> <p>Pregnant age: NR (NR) NR</p> <p>Race of Mother: White European (8.5) Black (10.6) Asian (4.3) Minority (Puerto Rican/Latino 66%; Afriecan - other 8.5%; Other or mixed ethnicity = 2%)</p>	<p>Inclusion Criteria: Healthy pregnant women, mid-pregnancy (20–24 weeks)</p> <p>Exclusion Criteria: parity .5; history of chronic hypertension; hyperlipidaemia; renal or liver disease; heart disease; thyroid disorder; multiple gestations; having been pregnant or lactating in the previous 2 years.</p>	<p>Start time: Pregnant 20-24 wk of gestation</p> <p>Duration: Pregnant until birth</p> <p>Arm 1: Placebo Description placebo bars (Manufacturer Nestec Limited (Vevey, Switzerland) Dose 5 placebo bars per week Blinding NR</p> <p>Arm 2: DHA-FF Description DHA cereal-based bars Manufacturer Nestec Limited (Vevey, Switzerland) Dose 5DHA cereal-based bars per week DHA 241 mg/d EPA 30.1 mg/d</p>	<p>Outcome gestational age Follow-up time birth Arm 1 Sample size 25 mean 39.4 SD (1.2) Arm 2 Sample size 22 mean 39.9 SD (1.1)</p>
<p>Harper et al., 2010⁴³</p> <p>Study name: NR</p> <p>Study dates: 01. 2005 - 10. 2006</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government,</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 852 Pregnant withdrawals 0 Pregnant completers 852</p> <p>Pregnant age: n3: 28 placebo 27 n3 23-32; placebo 24-32</p> <p>Race of Mother: White European (n3: 56.5; placebo 57.7) Black (n3:</p>	<p>Inclusion Criteria: a documented history of at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation</p>	<p>Start time: Pregnant 16-22 week gestation age</p> <p>Duration: Pregnant 36 weeks of gestation</p> <p>Arm 1: placebo Description inert mineral oil Manufacturer Eminent Services, Frederick, MD Active ingredients 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose four capsules of matching oil containing a minute amount of inert mineral oil Blinding Boxes containing a woman's entire supply of capsules in blister packs were sequentially</p>	<p>Outcome gestational age Follow-up time birth Arm 1 Sample size 418 mean 37.4 range (35.7-38.7) Arm 2 Sample size 434 mean 37.7 range (36-39) Outcome incidence of premature birth Follow-up time birth Arm 1 174/418 (41.6%) Arm 2 164/434 (37.8%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Manufacturer supplied product Follow-up article(s) ⁴⁷	34.1; placebo 34.9) Asian (n3: 3, placebo 1.2) Hispanic (n3: 14.7; placebo 13.6) Other race/ethnicity (NR)	Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	numbered according to the predetermined randomization sequence, and on enrollment a woman was assigned the next number in sequence. Study group assignment was not known by study participants, their health care providers, or the research personnel Arm 2: Eminent Services, Frederick, MD Active ingredients 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose in 4 capsules total 2000 mg of n3 DHA 800 mg EPA 1200 mg	
Judge et al., 2007 ³⁸ Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government, None	Study Population: Healthy pregnant women Pregnant enrolled 29 Pregnant completers 29 Pregnant age: 23.75 years (.4 years) NR Race of Mother: NR (100%)	Inclusion Criteria: women aged 18 –35 y who were at 20 wk of gestation Exclusion Criteria: Women with a history of drug or alcohol addiction, hypertension, smoking, hyperlipidemia, renal disease, liver disease, diabetes, or psychiatric disorder	Start time: Pregnant 24 weeks gestation Duration: Pregnant until birth Arm 1: placebo Description cereal based placebo bars Manufacturer Nestec? Active ingredients 18 g carbohydrates, 1.3 grams protein, 92 calories, 1.7 g fat Viability NR Dose 5 bars per week Blinding NR Arm 2: DHA supplemented cereal bars Manufacturer Nestec? Active ingredients 18 g carbohydrates, 1.3 grams protein, 92 calories, 1.7 g fat Viability NR Dose 5 bars per week. DHA-containing cerealbased bars [1.7 g total fat, 300 mg DHA as low-eicosapentaenoic oil (EPA) fish oil; EPA:DHA 1:8 per bar DHA mg/d EPA .75 mg (calculated based on EPA:DHA ratio) EPA-DHA 1:8	Outcome gestational age Follow-up time birth Arm 1 Sample size 15 mean 39 SD (1) Arm 2 Sample size 14 mean 39.9 SD (0.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Judge et al., 2012³⁹</p> <p>Study name: NR</p> <p>Study dates: nr</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: NR</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 48</p> <p>Pregnant age: Treatment group: 23.93 Placebo: 23.86 (Treatment group: 4.32 Placebo: 4.53)</p> <p>Race of Mother: White European (Treatment: 11.1%, Placebo: 0%) Black (Treatment: 18.5%, Placebo: 4.8%) Asian (Treatment: 3.7%, Placebo: 0%) Hispanic (Treatment: 59.3%, Placebo: 80.9%) NR (Treatment: 7.4%, 3 (14.3%))</p>	<p>Inclusion Criteria: The women were either primiparous or had not been pregnant for the past 2 years.</p> <p>Exclusion Criteria: parity greater than 5, history of chronic hypertension, hyperlipidemia, renal, liver or heart disease, thyroid disorder, multiple gestations or pregnancy induced complications including hypertension, preeclampsia or preterm labor, smoking and psychiatric disorders. Women who were treated during labor with analgesics such as Stadol (butorphanol tartrate), that may cause infant respiratory distress were also excluded. In addition, infants born preterm and infants with less than 4 h of crib time in the first and second days postpartum were excluded from the analyses.</p>	<p>Start time: Pregnant 24 weeks gestation</p> <p>Duration: Pregnant until delivery</p> <p>Arm 1: Placebo Description Control group Manufacturer estec, S.A., Switzerland Blinding The total macronutrient content was the same in both the DHA and placebo bars with respect to carbohydrate, protein and fat, however, the DHA bars contained fish oil (300 mg DHA) and the placebo bars contained corn oil.</p> <p>Arm 2: DHA Description Intervention group Manufacturer estec, S.A., Switzerland Dose average of 5 bars weekly DHA 300 mg EPA-DHA 8:1 ratio of DHA to EPA</p>	<p>Outcome gestational age Follow-up time birth Arm 1 Sample size 21 mean 39.19 SD (1.17) Arm 2 Sample size 27 mean 39.72 SD (1.2)</p>
<p>Lucia Bergmann et al., 2007⁴⁰</p> <p>Study name: NR</p> <p>Study dates: 2000-2002</p> <p>Study design: Trial randomized parallel</p> <p>Location: Germany</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 144 Pregnant withdrawals 51 Pregnant completers 69</p> <p>Pregnant age: 31 (DHA 4.69; control 4.89)</p> <p>Infant age: DHA 39.1;</p>	<p>Inclusion Criteria: at least 18 years of age and willing to breastfeed for at least three months were enrolled at 21 weeks' gestation during the period October 2000 to August 2002</p> <p>Exclusion Criteria: increased risk of premature delivery or</p>	<p>Start time: Pregnant 21th week</p> <p>Duration: Pregnant 37th week</p> <p>Arm 1: Vitamins and minerals Manufacturer Nestle' (Vevey, Switzerland) Arm 2: Prebiotic Description basic supplement plus the prebiotic, fructooligosaccharide (FOS) (4.5 g) Manufacturer Nestle' (Vevey, Switzerland) Active ingredients fructooligosaccharide (FOS) (4.5 g)</p>	<p>Outcome gestational age Follow-up time birth Arm 1 Sample size 74 mean 39.5 SD (1.38) Arm 3 Sample size 43 mean 39.1 SD (1.64)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: NR	control 39.5 weeks (DHA 1.64; control 1.38) Race of Mother: White European (100)	multiple pregnancy, allergy to cow milk protein, lactose intolerance, diabetes, smoking, consumption of alcohol (>20 g/week), or participation in another study. Infants excluded if they were premature at birth (<37 week gestation, or had any major malformations or hospitalized for more than one week.	Arm 3: DHA Description basic supplement with FOS and DHA (200 mg) Manufacturer Nestle (Vevey, Switzerland) Dose 200 mg DHA prepared from fish oil (assuming that some EPA but dose was not reported) DHA 200 mg EPA NR	
Mozurkewich et al., 2013 ⁴¹ Study name: NR Study dates: Oct 2008 - may 2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 126 Pregnant withdrawals 8 Pregnant completers 118 Pregnant age: EPA 29.9; DHA 30.6; placebo 30.4 (EPA 5.0; DHA 4.5; placebo 5.9) Race of Mother: White European (85%; 76%; 83%) Black (10%; 11%; 5%) Asian (3%; 3%; 2%) Hispanic (0%; 11%; 7%) Inuit Eskimo (0%; 0%; 2%) Pacific Islander (NR)	Inclusion Criteria: past history of depression, an EPDS score 9-19 (at risk for depression or mildly depressed), singleton gestation, a maternal age of 18 years or older, and a gestational age of 12-20 weeks Exclusion Criteria: had a history of a bleeding disorder, thrombophilia requiring anticoagulation, multiple gestation, bipolar disorder, current major depressive disorder, current substance abuse, lifetime substance dependence, or schizophrenia. Women were also ineligible if they were currently taking omega-3 fatty acid supplements or antidepressant medications or eating more than 2 fish meals per week.	Start time: Pregnant 12-20 week gestation Duration: Pregnant assuming till birth Arm 1: Control/Placebo Description 98% soy oil and 1% each of lemon and fish oil Manufacturer Nordic Naturals Corporation in Watsonville, CA Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose 2 large and 4 small placebo capsules Blinding The placebos were formulated to be identical in appearance to both the EPA- and DHA-rich supplements Arm 2: EPA-rich fish oil Description an approximate 4:1 ratio of EPA to DHA (1060 mg EPA plus 274 mg DHA) Brand name ProEPAXtra, Nordic Naturals Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose 2 large EPA capsule and 4 small placebo DHA 274 mg EPA 1060 mg Arm 3: DHA-rich fish oil Description DHA and EPA in an approximate 4:1 ratio of (900 mg DHA plus 180 mg EPA) Brand name ProDHA, Nordic Naturals Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C.	Outcome gestational age Follow-up time birth Arm 1 Sample size 41 mean 39.1 SD (1.5) Arm 2 Sample size 39 mean 39.1 SD (1.5) Arm 3 Sample size 38 mean 40.4 SD (0.9)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Dose 2 large placebo oil and 4 small DHA rich DHA 900 mg EPA 180 mg	
Pietrantoni et al., 2014 ²⁹ Study name: NR Study dates: nr Study design: Trial randomized parallel Location: Italy Funding source / conflict: Government	Study Population: Healthy pregnant women Pregnant enrolled 300 Pregnant completers 255 Pregnant age: DHA 30.86 +-4.18/placebo group 29.92+-4.8 Race of Mother: NR (NR)	Inclusion Criteria: caucasians 22 to 35 yrs, 8 week gestational age, single pregnancy, BMI between 18.5 and 25.0kg/m2, habitual fish consumption (twice a week at least), high school or university degree, average socioeconomic status, absence of uterine abnormalities (fibroids, cervical incompetence, uterine malformations etc) Exclusion Criteria: smoking, substance abuse including alcohol, allergy to fish or derivates, diabetes, hypertension, metabolic, cardiovascular, renal, psychiatric, neurologic, throbophilic, thyroid or autoimmune diseases, previous pregnancy complications (miscarriage, preterm or operative delivery), previous uterine sugery, recurrent genito-urinary infections	Start time: Pregnant 8th weeks Duration: Pregnant 8th week to delivery Arm 1: Placebo Description Olive oil Arm 2: DHA group Description DHA capsule Dose 2* 100mg capsule DHA 100mg * 2 capsule	Outcome preterm-premature rupture of membranes Follow-up time birth Arm 1 4/126 (3.2%) Arm 2 1/129 (0.8%)
Stein et al., 2011 ³³ Study name: NR Study dates: 02. 2005-02.2007	Study Population: Healthy infants Pregnant enrolled 1094 Pregnant completers 973	Inclusion Criteria: women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively	Start time: Pregnant 18-22 Gestinal week Infants birth Duration: Pregnant birth Arm 1: Placebo	Outcome gestational age Follow-up time birth Arm 1 Sample size 368 mean 39.1 SD (1.6) Arm 2 Sample size 369 mean 39.1 SD (1.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study design: Trial randomized parallel</p> <p>Location: Mexico</p> <p>Funding source / conflict: Government</p>	<p>Pregnant age: placebo 26.3; DHA 26.4 (placebo 4.6; DHA 4.9)</p> <p>Infant age: 39.1 (placebo 1.6; DHA 1.8)</p> <p>Race of Mother: NR</p>	<p>or predominantly breast-fed for at least 3 mo, and to live in the area for at least 2 y after delivery</p> <p>Exclusion Criteria: NR</p>	<p>Description Olive oil Manufacturer Martek Biosciences Dose 2 capsules olive oil Blinding Similar in appearance and taste to DHA capsules Arm 2: DHA Description algal DHA capsules Manufacturer Martek Biosciences Dose 2 capsules * 200mg DHA 400 mg</p>	<p>Outcome incidence of premature birth Follow-up time birth Arm 1 30/368 (8.2%) Arm 2 33/369 (8.9%)</p>
<p>Ramakrishnan et al., 2010³¹</p> <p>Study name: POSGRAD</p> <p>Study dates: feb 2005 - feb 2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: Mexico</p> <p>Funding source / conflict: Government, March of Dimes</p> <p>Follow-up: 840</p> <p>Follow-up article(s) ^{32, 72}</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 1,094 Pregnant withdrawals 67 Pregnant completers 973 (for birthweight)</p> <p>Pregnant age: 26.2 (controls) 26.3 (DHA) (4.6 (controls) 4.8 (DHA))</p> <p>Race of Mother: Hispanic (NR)</p>	<p>Inclusion Criteria: 18-35 yrs. of age, in gestation weeks 18-22, planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breastfed for at least 3 months, liver in the area for at least 2 years after delivery.</p> <p>Exclusion Criteria: high-risk pregnancy; lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplements; chronic use of certain medications (e.g., medications for epilepsy).</p>	<p>Start time: Pregnant at study entry</p> <p>Duration: Pregnant mid pregnancy (18-22 weeks gestation) until delivery</p> <p>Arm 1: Controls Description Placebo containing olive oil Manufacturer Martek Biosciences Dose 1 capsule, twice a day Blinding Identical tablets Arm 2: DHA Description Intervention Manufacturer Martek Biosciences N-3 Composition 200 mg DHA derived from algal source Dose 1 capsule twice a day DHA 400 mg/d</p>	<p>Outcome gestational age Follow-up time birth Arm 1 Sample size 486 mean 39.1 SD (1.7) Arm 2 Sample size 487 mean 39 SD (1.9) Outcome incidence of premature birth Follow-up time birth Arm 1 40/486 (8.3%) Arm 2 49/487 (10.1%)</p>
<p>Stein et al., 2012³²</p> <p>Study name: POSGRAD</p> <p>Study dates: Feb 2005- Feb 2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: NR</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 1094 Pregnant withdrawals 63 Pregnant completers 900</p> <p>Pregnant age: 26.3 (4.6-4.8)</p>	<p>Inclusion Criteria: Singleton live births without congenital anomalies</p> <p>Exclusion Criteria: 3364: high risk pregnancy, (history and prevalence of pregnancy complications, including abruptio placentae,</p>	<p>Start time: Pregnant 18-22 wk</p> <p>Duration: Pregnant to birth</p> <p>Arm 1: Placebo Description A mixture of corn and soy oil Manufacturer Martek Biosciences Blinding "Participants and members of the study team were unaware of the treatment scheme throughout the intervention period of the study" Arm 2: DHA</p>	<p>duplicate data of id 3364</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Funding source / conflict: Government</p> <p>Follow-up: 3364</p> <p>Follow-up article(s) ³¹, ⁷²</p>	<p>Infant age: 39.1 (1.7-1.8)</p> <p>Race of Mother: NR (NR)</p>	<p>preeclampsia, pregnancy-induced hypertension, any serious bleeding episode in the current pregnancy, and physician referral); lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplement, or chronic use of certain medication(eg. epilepsy medications)</p>	<p>Description DHA 400 mg/d</p> <p>Manufacturer Martek Biosciences</p> <p>Dose 2 capsule per day</p> <p>DHA 2*200mg</p>	

Table 2. Observational Studies for Length of Gestation (or Gestational Age) and Preterm Birth

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Badart-Smook, et al., 1997⁴⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: NR</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 610 Pregnant withdrawals 240 Pregnant completers 370</p> <p>Pregnant age: 29 (4)</p> <p>Race of Mother: White European (100)</p>	<p>Inclusion Criteria: White race, intention to give birth to the baby in one of the three hospitals involved in the study</p> <p>Exclusion Criteria: Women with diastolic blood pressure of 90mm or higher, women suffering from any metabolic, cardiovascular, neurological, or renal disorder</p>
<p>Klebanoff, et al., 2011⁴⁷</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: US</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 7906</p> <p>Follow-up article(s) ⁴³</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 852 Pregnant completers 852</p> <p>Pregnant age: <1/month, 27.1 (5.6) 0.5-3 per week, 28.0 (5.6) >3 per week, 27.3 (5.7) (<1/month, 27.1 (5.6) 0.5-3 per week, 28.0 (5.6) >3 per week, 27.3 (5.7))</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation</p> <p>Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation</p>
<p>Oken, et al., 2004⁴⁵</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 2109 Pregnant completers 2109</p> <p>Pregnant age: 14-<20, 3% 20-<25, 6% 25-<30, 21% 30-<35, 42% 35=<40, 23% >=40, 4% (14-44)</p>	<p>Inclusion Criteria: delivered a live infant, and completed at least one dietary questionnaire</p> <p>Exclusion Criteria: taking cod liver or fish oil supplement</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
Location: US Funding source / conflict: Government, Multiple foundations and Societies	Race of Mother: White European (66) Black (16) Asian (6) Hispanic (7) Other race/ethnicity (4)	

Gestational Hypertension and Preeclampsia

Because a number of studies identified for this report combined the outcomes of gestational hypertension (GHTN), preeclampsia (PE), and eclampsia, we report them together.

Key Findings and Strength of Evidence for Risk for Gestational Hypertension/Preeclampsia

- Pooled analysis of three RCTs found no effect of fish oil intake during pregnancy on the risk for gestational hypertension or preeclampsia among women at increased risk for poor pregnancy outcomes.
- Pooled analysis of three RCTs (n=2,875) assessing the effects of DHA alone or DHA-enriched fish oil on the risk for GHTN/PE among women not at increased risk showed no effects.
- One study that assessed the effects of EPA alone on women not at risk showed no effect.
- No studies of ALA supplementation were found.
- Four prospective observational studies that assessed the association between n-3 intake and risk for GHTN or PE showed no consistent associations. One study that assessed the association of biomarkers for n-3 intake with risk for GHTN/PE showed no association.

Randomized Controlled Trials

The original report identified 8 RCTs that assessed the effects of supplementation of pregnant women with n-3s on the outcomes of GHTN and/or PE. Pooling the outcomes of two trials on the effects of fish oil on the risk for GHTN among women at increased risk for GHTN or other high-risk pregnancy outcomes (N=582) revealed a non-statistically significant increase in the risk for GHTN among n-3 supplemented women (OR 1.07 [0.75, 1.51]).

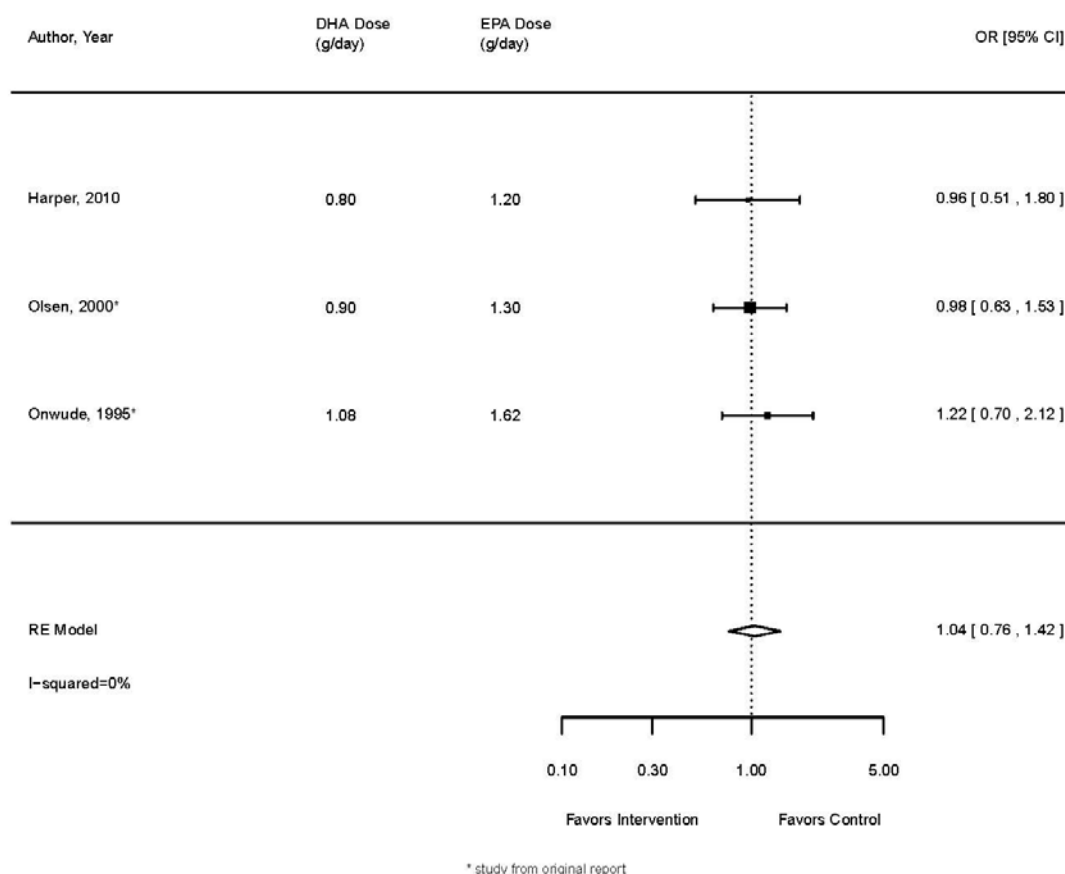
Four RCTs identified for the current report assessed the effects of n-3s on risk for GHTN and/or PE (see Table 3).^{30, 41, 43, 49} Three of these RCTs enrolled women with no prior risk of poor pregnancy outcomes (N=2,875) (although one of the studies enrolled women at increased risk for peripartum depression).^{30, 41, 49} The fourth RCT, by Harper and colleagues (2012), enrolled 852 women with a history of recurrent preterm birth.⁴³

Marine oil vs. placebo

Population at risk for poor pregnancy outcomes

Meta-analysis of the two RCTs from the original report, which compared the effects of marine oil versus placebo on at-risk populations, and the newly identified RCT by Harper and colleagues, which compared the effects of a mixture of EPA and DHA derived from fish with that of mineral oil among an at-risk population,⁴³ yielded a non-significant summary effect size for risk of GHTN or preeclampsia (OR [95% CI]=1.04 [0.76, 1.42], $I^2=0\%$) (see Figure 9).

Figure 9. Pregnancy induced hypertension/preeclampsia – DHA + EPA vs. placebo



The latter study also administered intra-muscular alpha-medroxyprogesterone caproate (the primary outcome of interest was prevention of preterm birth) and the fish oil capsules contained vitamin E as a preservative.

The study by Harper and colleagues conducted a subgroup analysis to determine whether the outcomes were affected by fish intake. No differences in outcomes were observed between women who consumed no fish or less than one serving of fish per month and those who consumed more fish.⁴³

Population not at risk for poor pregnancy outcomes

No studies were identified that assessed the effects of marine oil compared with placebo on the risk for GHTN or PE among women not at risk for poor pregnancy outcomes.

DHA vs. placebo

Population at risk for poor pregnancy outcomes

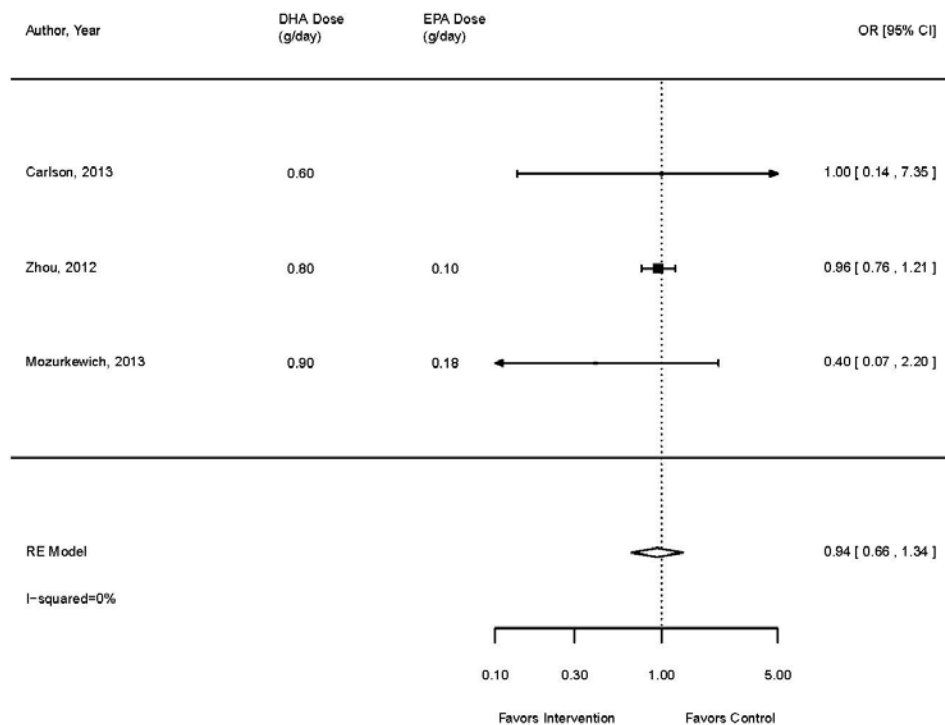
We identified no studies that compared the effect of supplements containing only DHA to that of placebo on the risk for GHTN or PE among women at increased risk for poor pregnancy outcomes.

Populations not at risk for poor pregnancy outcomes

We identified three RCTs that compared the effect of supplements containing only DHA (600 to 900 mg/day) to that of placebo on the risk for GHTN or PE among women at increased risk for poor pregnancy outcomes. The DOMInO trial enrolled 2,399 pregnant Australian women (less than 21 weeks gestation) to receive 800 mg/day DHA-enriched fish oil or vegetable oil placebo and followed throughout the second half of pregnancy to assess risk for gestational diabetes and PE as primary outcomes. No differences were seen in the risk for PE (adjusted or unadjusted for clinic and parity).⁴⁹ The Mothers, Omega-3, and Mental Health Study enrolled 126 pregnant U.S. women at risk for depression and randomly assigned them to receive DHA-enriched fish oil (900 mg DHA:180 mg EPA/day), EPA-enriched fish oil (1,060 mg EPA:274mg DHA), or soy bean oil placebo from early gestation through term. No differences were seen among groups in risk for development of GHTN or PE.⁴¹ Finally, Carlson and coworkers randomized 350 pregnant U.S. women at less than 21 weeks gestation to receive 600mg/day DHA from marine algal oil or soybean and corn oil through term. No differences were seen between groups in the secondary outcome PE.³⁰

Meta-analysis of the three RCTs yielded a non-significant summary effect size for DHA supplementation and risk of GHTN or preeclampsia (OR [95% CI]=0.94[0.66, 1.34], $I^2=0\%$)(Figure 10).

Figure 10. Pregnancy induced hypertension/preeclampsia – DHA vs. placebo



EPA vs. placebo

Only one RCT was identified that compared the effects of EPA supplementation with that of placebo on the risk for GHTN or PE. This study, described above, found no significant difference between EPA-enriched fish oil, DHA-enriched fish oil, and placebo and the risk for developing GHTN or PE.⁴¹

ALA vs. placebo

We identified no studies that assessed the effects of ALA supplementation on risk for GHTN or PE.

Observational Studies

Four prospective studies evaluated the association between some measure of n-3 FA exposure and risk for GHTN or PE.⁷³⁻⁷⁶ All enrolled populations of healthy pregnant women, usually at their first prenatal visit. One study was a nested case-control from a large RCT that assessed the association between dietary intakes of n-3 FA and maternal biomarkers and risk for GHTN.⁷³ The remainder were prospective cohort studies that assessed the association between

dietary intakes of n-3 FA and risk for GHTN or PE.⁷⁴⁻⁷⁶ (Table 4) Publications dated from 1995 to 2007.

n-3 FA Intake

Four studies evaluated the association between n-3 FA intake and risk for GHTN and/or PE.⁷³⁻⁷⁶

A 1995 study assessed the association of n-3 FA intakes with risk for GHTN among a cohort of 208 healthy pregnant women in the Netherlands who enrolled in a RCT at less than 16 weeks gestation (52 of 208 women developed GHTN).⁷³ Intake of n-3 FA was established based on use of FFQ (and dietary history as a double check). No differences were observed in total n-3 FA intake between women who subsequently developed GHTN and those who did not.

A 2001 study of 3,133 healthy Norwegian women who completed a validated FFQ found a slight but significant increase in the risk for PE associated with increasing intakes of n-3 FA and n-6 FA, adjusted for age, smoking status, BMI, systolic blood pressure, and parity.⁷⁴ Further adjustment for energy intake resulted in these trends no longer being significant.

A 2006 study followed 488 healthy Icelandic women: 30 developed GHTN and 19 developed PE. Analysis of responses to a semi-quantitative food and lifestyle questionnaire showed that women who consumed cod liver oil early in pregnancy were almost 5 times as likely to develop GHTN or PE than women who did not (adjusted OR 4.7, [1.8, 12.6] p=0.002). Cod liver oil is a source of vitamins A, D, and E as well as n-3 FA. A slight U-shaped association was seen between daily intakes of n-3FA and risk for GHTN or PE or GHTN alone (p=0.008).⁷⁶

Project Viva, a U.S. study, followed 1,718 pregnant women, 59 of whom developed PE (3%) and 119 who developed GHTN (7%). Multivariate logistic regression analysis of a modified validated semi-quantitative FFQ showed a slightly *decreased* risk for PE with higher intakes of DHA + EPA (adjusted OR 0.84 [0.69, 1.03] per 100 mg per day) and DHA+EPA: AA (adjusted OR 0.82 [0.66, 1.01]) but not for GHTN. No association was seen for intakes of ALA.⁷⁵

n-3 FA Biomarkers

One of the studies described above assessed the association between biomarkers for n-3s and the risk for GHTN.⁷³ No significant differences were found at any point during pregnancy in any of the maternal plasma phospholipid n-3 FA or n-6 FA between women who developed GHTN and those who did not. However postnatal plasma phospholipids of women with GHTN showed lower levels of ALA and LA than did those of women with normal pregnancies.

Observational study subgroup analyses

None of the studies reported subgroup analyses.

Table 3. RCTs for Gestational hypertension preeclampsia eclampsia

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Zhou et al., 2012⁴⁹</p> <p>Study name: DOMInO</p> <p>Study dates: 10. 2005 - 01. 2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up article(s)^{34, 48, 50, 51, 52, 53, 3}</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 2399</p> <p>Race of Mother: White European (88%;88%) Asian (7%;8%) Inuit Eskimo (2%;1%) Other race/ethnicity (NR)</p>	<p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: If already taking a dietary supplement containing DHA, their fetus had a known major abnormality, they had a bleeding disorder for which fish oil was contraindicated, they were receiving anticoagulant therapy, they had a documented history of drug or alcohol abuse, they were participating in another fatty acid trial, or English was not the main language spoken at home</p>	<p>Start time: Pregnant medium gestation age 19 weeks</p> <p>Duration: Pregnant birth</p> <p>Arm 1: control Description 500-mg vegetable oil capsules Dose 3*500mg 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Blinding All capsules were similar in size, shape, and color</p> <p>Arm 2: DHA Description DHA-rich fish oil Manufacturer Incromega 500 TG; Croda Chemicals Dose 3*500mg capsule DHA 800 mg EPA 100 mg</p>	<p>Outcome preeclampsia</p> <p>Follow-up time during pregnancy</p> <p>Arm 1 58/1202 (4.85%)</p> <p>Arm 2 60/1197 (4.97%)</p> <p>Outcome pregnancy induced hypertension</p> <p>Follow-up time during pregnancy</p> <p>Arm 1 107/1202 (8.88%)</p> <p>Arm 2 98/1197 (8.18%)</p>
<p>Carlson et al., 2013³⁰</p> <p>Study name: NR</p> <p>Study dates: 2006.01-2011.10</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 350 Pregnant withdrawals 49 Pregnant completers 301</p> <p>Pregnant age: placebo: 24.8; DHA: 25.3 (placebo 4.7; DHA 4.9)</p> <p>Race of Mother: Black (46%;37%) Non-black (54%; 63%)</p>	<p>Inclusion Criteria: Englishspeaking, between 8 and 20 wk of gestation, between 16 and 35.99 y of age, and planning to deliver at a hospital in the Kansas City metropolitan area</p> <p>Exclusion Criteria: carrying more than one fetus, had preexisting diabetes mellitus or systolic blood pressure \$140 mm Hg at enrollment, or had any serious health condition likely to affect the prenatal or postnatal</p>	<p>Start time: Pregnant 99.6/102.9 day</p> <p>Duration: Pregnant enrollment to birth</p> <p>Arm 1: Placebo Description half soybean and half coin oil Manufacturer DSM Nutritional Products) Active ingredients a-linolenic acid Dose 3 *capsule 200/day Blinding both DHA and placebo capsules were orange flavored</p> <p>Arm 2: DHA Description marine algae-oil source of DHA Manufacturer DHASCO; DSM Nutritional Products, formerly Martek Biosciences) Dose 200 mg capsule, 3 times a day DHA 200mg/capsule * 3</p>	<p>Outcome preeclampsia</p> <p>Follow-up time during pregnancy</p> <p>Arm 1 2/147 (1.3%)</p> <p>Arm 2 2/154 (1.3%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		growth and development of their offspring, including cancer, lupus, hepatitis, HIV/AIDS, or a diagnosed alcohol or chemical dependency. or if the initial screening based on their self-reported weight and height suggested a BMI (in kg/m2 ≥ 40).		
<p>Harper et al., 2010⁴³</p> <p>Study name: NR</p> <p>Study dates: 01. 2005 - 10. 2006</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up article(s) ⁴⁷</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 852 Pregnant withdrawals 0 Pregnant completers 852</p> <p>Pregnant age: n3: 28 placebo 27 n3 23-32; placebo 24-32</p> <p>Race of Mother: White European (n3: 56.5; placebo 57.7) Black (n3: 34.1; placebo 34.9) Asian (n3: 3, placebo 1.2) Hispanic (n3: 14.7; placebo 13.6) Other race/ethnicity (NR)</p>	<p>Inclusion Criteria: a documented history of at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation</p> <p>Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either</p>	<p>Start time: Pregnant 16-22 week gestation age</p> <p>Duration: Pregnant 36 weeks of gestation</p> <p>Arm 1: placebo Description inert mineral oil Manufacturer Eminent Services, Frederick, MD Active ingredients 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose four capsules of matching oil containing a minute amount of inert mineral oil Blinding Boxes containing a woman's entire supply of capsules in blister packs were sequentially numbered according to the predetermined randomization sequence, and on enrollment a woman was assigned the next number in sequence. Study group assignment was not known by study participants, their health care providers, or the research personnel</p> <p>Arm 2: Eminent Services, Frederick, MD Active ingredients 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose in 4 capsules total 2000 mg of n3 DHA 800 mg EPA 1200 mg</p>	<p>Outcome preeclampsia or gestational hypertension</p> <p>Follow-up time during pregnancy</p> <p>Arm 1 20/418 (4.8%)</p> <p>Arm 2 20/434 (4.6%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		elsewhere or before 37 weeks of gestation		
<p>Mozurkewich et al., 2013⁴¹</p> <p>Study name: NR</p> <p>Study dates: Oct 2008 - may 2011</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 126 Pregnant withdrawals 8 Pregnant completers 118</p> <p>Pregnant age: EPA 29.9; DHA 30.6; placebo 30.4 (EPA 5.0; DHA 4.5; placebo 5.9)</p> <p>Race of Mother: White European (85%; 76%; 83%) Black (10%; 11%; 5%) Asian (3%; 3%; 2%) Hispanic (0%; 11%; 7%) Inuit Eskimo (0%; 0%; 2%) Pacific Islander (NR)</p>	<p>Inclusion Criteria: past history of depression, an EPDS score 9-19 (at risk for depression or mildly depressed), singleton gestation, a maternal age of 18 years or older, and a gestational age of 12-20 weeks</p> <p>Exclusion Criteria: had a history of a bleeding disorder, thrombophilia requiring anticoagulation, multiple gestation, bipolar disorder, current major depressive disorder, current substance abuse, lifetime substance dependence, or schizophrenia. Women were also ineligible if they were currently taking omega-3 fatty acid supplements or antidepressant medications or eating more than 2 fish meals per week.</p>	<p>Start time: Pregnant 12-20 week gestation</p> <p>Duration: Pregnant assuming till birth</p> <p>Arm 1: Control/Placebo Description 98% soy oil and 1% each of lemon and fish oil Manufacturer Nordic Naturals Corporation in Watsonville, CA Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose 2 large and 4 small placebo capsules Blinding The placebos were formulated to be identical in appearance to both the EPA- and DHA-rich supplements</p> <p>Arm 2: EPA-rich fish oil Description an approximate 4:1 ratio of EPA to DHA (1060 mg EPA plus 274 mg DHA) Brand name ProEPAXtra, Nordic Naturals Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose 2 large EPA capsule and 4 small placebo DHA 274 mg EPA 1060 mg</p> <p>Arm 3: DHA-rich fish oil Description DHA and EPA in an approximate 4:1 ratio o (900 mg DHA plus 180 mg EPA) Brand name ProDHA, Nordic Naturals Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose 2 large placebo oil and 4 small DHA rich DHA 900 mg EPA 180 mg</p>	<p>Outcome gestational hypertension or preeclampsia Follow-up time during pregnancy Arm 1 5/41 (12%) Arm 2 8/39 (21%) Arm 3 2/38 (5%)</p>

Table 4. Observational studies for Gestational hypertension preeclampsia eclampsia

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Oken, et al., 2007⁷⁵</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: US</p> <p>Funding source / conflict: Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant age: 93% were 20-40 years</p> <p>Race of Mother: White European (72%) Black (12%) Hispanic (6%) Other race/ethnicity (10%)</p>	<p>Inclusion Criteria: 1st trimester pregnant women attending 1st prenatal visit</p> <p>Exclusion Criteria: Post hoc: no live birth, no medical records, failure to complete dietary questionnaires, pre-existing chronic hypertension and no subsequent preeclampsia</p>
<p>Clausen, et al., 2001⁷⁴</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Norway</p> <p>Funding source / conflict: NR</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 3,771 Pregnant completers 3,133</p> <p>Pregnant age: 29.8 (4.5)</p> <p>Race of Mother: White European (100)</p>	<p>Inclusion Criteria: Caucasian women seen at Aker University Hospital for prenatal care and who agreed to undergo ultrasound at their first prenatal visit and who completed a FFQ</p> <p>Exclusion Criteria: Pregestational diabetes, abortion, twin or triplet pregnancies, patients who give birth at other hospitals, missing records, loss to followup</p>
<p>Olafsdottir, et al., 2006⁷⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: NR</p> <p>Funding source / conflict: Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 549 Pregnant completers 488</p> <p>Pregnant age: 28 (5)</p> <p>Race of Mother: White European (NR)</p>	<p>Inclusion Criteria: Pregnant women attending first prenatal visit at Center of Prenatal Care in Reykjavik</p> <p>Exclusion Criteria: Essential hypertension, gestational diabetes, miscarriage/stillbirth, twins/triplets, preterm birth, loss of personal data, moved, missing data,</p>

Small for Gestational Age, Intrauterine Growth Retardation, and Low Birth Weight

Low Birth Weight

Key Findings and Strength of Evidence for Risk of Low Birth Weight

- There is a low level of evidence that maternal supplementation of DHA may not have significant effects on risk for delivering a low birth weight infant.
 - Pooled analyses of 3 RCTs assessing the effects of DHA alone or DHA-enriched fish oil on the risk of delivering a LBW infant among women not at increased risk showed no significant effects.
 - One RCT assessing the effect of DHA+EPA on the risk of delivering a LBW infant among women at increased risk showed no significant effects.
 - One prospective observational study assessing the effect of EPA intake in the third trimester of pregnancy on LBW found a significantly increased risk among women in the first and second tertiles of EPA intake. No associations were seen between tertiles of EPA intake and risk of LBW in the first or second trimesters of pregnancy.

Description of Included Studies

The original report included three RCTs that assessed the effects of maternal n-3 FA intake on the outcome of intrauterine growth retardation (IUGR) and seven RCTs that assessed the effects of maternal n-3 FA intake on the outcome of low birth weight (LBW, defined as <2,500 or as <2,000 grams). Two RCTs assessed both IUGR and LBW outcomes. For the IUGR outcome, all three RCTs enrolled pregnant women at risk of IUGR, due to a previous history of IUGR, twin pregnancy, or history of premature delivery. Meta-analysis of these three RCTs found no significant effects of DHA+EPA supplementation (doses ranged from 2.2 to 3 g/d) on the incidence of IUGR (birth weight < 3rd and 10th percentile, adjusted for gestational age [GA]) between DHA+EPA supplementation and control groups (OR: 1.14, 95% Confidence Interval [CI] 0.79; 1.64). Of the seven RCTs that assessed LBW outcomes, two compared n-3 FA-enriched eggs (DHA 0.23 g/d) with control eggs and the other five compared fish oil (DHA+EPA) supplements with placebo. Five of the seven RCTs showed that n-3 FA supplementation did not influence the incidence of LBW infants among pregnant women with or without a history of previous IUGR. The other two RCTs each found a lower incidence of LBW infants born to women who received fish oil (DHA+EPA) supplements compared with those who received placebo (-26% and -1.9%).

For the current report, we identified four RCTs (in 7 publications)^{30-34, 43, 49} and one observational study⁷⁷ that assessed the effects of maternal n-3 FA intake on risk of LBW. Three of these RCTs^{33, 43, 49} also assessed the effects of maternal n-3 intake on risk of small-for-gestational-age (SGA) or IUGR. In addition, two observational studies^{45, 78} examined the association of maternal n-3 FA exposure (dietary intake or plasma concentration) with risk for SGA/IUGR. In all studies, SGA or IUGR were both defined as birth weight for gestational age <10th percentile of a reference standard, and LBW was defined as birthweight <2,500 grams. Of the studies identified for the current report, all were conducted among healthy, pregnant women, except for one RCT that enrolled women who were identified as being at risk of having an SGA/IUGR outcome due to having at least one prior spontaneous preterm delivery⁴³.

Randomized Controlled Trials

Four RCTs (in seven publications) were identified for the current report that assessed the effects of n-3 FA interventions on LBW. Three of the publications were from the POSGRAD (Prenatal DHA (Omega-3 fatty acid) Supplements on infant GRowth And Development) trial³¹⁻³³ and two of the publications were from the Docosahexaenoic Acid to Optimise Mother Infant Outcome (DOMInO) trial^{34, 49}.

DHA

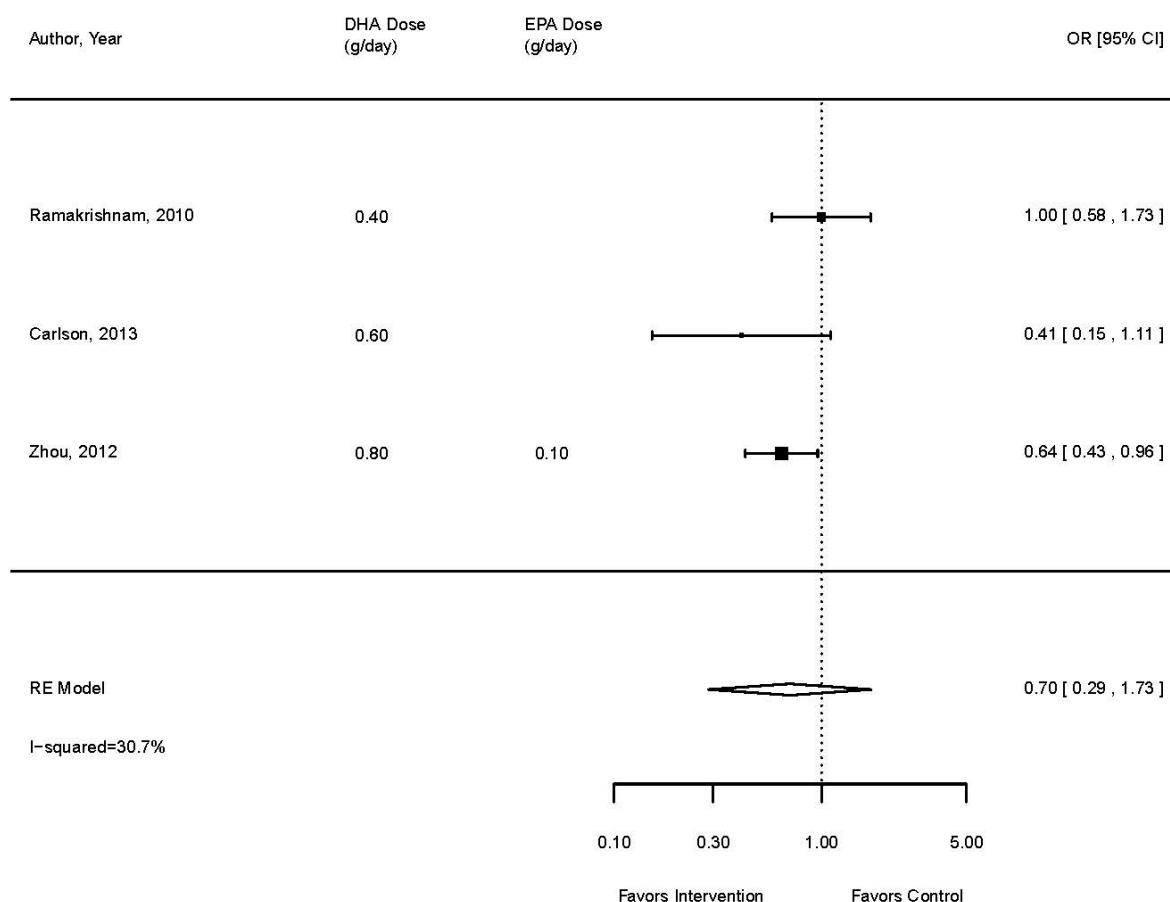
The POSGRAD trial randomized 1,094 pregnant Mexican women (18-22 weeks' gestation) to receive 0.4 g/day DHA or a placebo containing olive oil.³³ Data on birth outcomes were available for 973 women, of whom 487 were randomized to receive DHA and 486 were randomized to receive placebo. Overall, there was no difference in percent of women delivering LBW infants (percent LBW, 5.5 percent for DHA vs. 5.6 percent for placebo, $p=0.99$). However, when stratified by gravidity, the findings showed a trend towards lower percent LBW in the DHA group compared to the placebo group (3.3 percent DHA vs. 7.4 percent placebo, $p=.08$) among primigravidae women, but no difference among multigravidae women (6.9 percent DHA vs. 4.4 percent placebo, $p=0.18$). The percent of LBW infants was not different in the subset of infants with 18 month follow-up data³³ or the subset on whom measures of auditory or visual evoked potentials were obtained.³²

The DOMInO trial^{34, 49} randomized 2,399 healthy, pregnant Australian women (<21 weeks' gestation) to receive a DHA-rich fish oil concentrate containing 0.8 g/day DHA and 0.1 g/day EPA ($n=1197$) or a vegetable oil placebo ($n=1202$). Percent LBW differed significantly between the two groups (3.4 percent DHA vs. 5.3 percent placebo, $p=0.03$).

Carlson et al. randomized 350 healthy, pregnant women in the U.S. (8-20 weeks' gestation) to receive 0.6 g/day DHA or a placebo containing half soybean and half corn oil.³⁰ Of the 301 women with birth outcome data, 154 were randomized to DHA and 147 were randomized to placebo. The study observed a trend towards lower prevalence of risk for LBW in the DHA group compared to the placebo group (3.9 percent vs. 9.0 percent, $p=.059$). A significant difference was also observed in prevalence of infants born with very low birthweight (<1500 g) between the two groups (0 percent for DHA vs. 3.4 percent for placebo, $p=.026$).

A meta-analysis of three trials revealed a non-significant odds-ratio favoring the DHA group (OR [95% CI]=0.70 [0.29, 1.73], $I^2=30.7\%$). (Figure 11)

Figure 11. LBW – DHA vs. placebo



EPA+DHA

Harper et al (2010)⁴³ randomized 852 U.S. women who had at least one prior spontaneous preterm delivery to receive marine oils (0.8 g/day DHA plus 1.2 g/day EPA) or a mineral oil placebo. Capsules from both groups also contained 10 IU vitamin E per capsule and all women received weekly injections of 17 α -hydroxyprogesterone caproate. Among the 837 liveborn neonates with birthweight data available, 427 were randomized to the n-3 group and 410 were randomized to placebo. This study found no significant difference in percent LBW infants between the two groups (22 percent n-3 vs. 27 percent placebo, $p>.05$). There was also no difference in percent of infants born with birthweight <1500g between the two groups (6.1 percent n-3 vs. 7.1 percent placebo, $p>.05$).

Observational studies

Muthayya et al (2009) assessed the association between n-3 FA intake in the first, second, and third trimesters of pregnancy and LBW among 675 women (ages 17-40 and <20 weeks of gestation) receiving medical care at St. John's Medical College Hospital in Bangalore, India.⁷⁷ Additionally, erythrocyte membrane phospholipid FA status was measured in a random subsample of 150 women in each trimester. No association was observed between tertiles of EPA intake and LBW in the first or second trimesters of pregnancy. In the third trimester (n=419), women in the first and second tertiles of EPA intake had significantly increased risk of LBW compared to the highest tertile after adjusting for confounders (adjusted OR [AOR] 2.75, 95% CI 1.26-6.02 for tertile 1; AOR 2.54, 95% CI 1.17-5.50 for tertile 2). No significant effects were observed between erythrocyte FA status and risk of LBW in this study.

SGA / IUGR

Key Findings and Strength of Evidence for Risk for SGA/IUGR

- Two RCTs found no effect of DHA alone or DHA-enriched fish oil on SGA/IUGR outcomes.
- Pooled analyses of 4 RCTs assessing the effects of DHA+EPA on SGA/IUGR among women at increased risk found no significant effects.
- One prospective observational study found no association between intake of DHA+EPA intake and SGA outcome.
- One observational study among multiparous pregnant women found a two-fold increase in risk of SGA among women in the lowest quintile of plasma EPA concentration in early pregnancy compared to those in the middle quintile. There was no association between plasma DHA concentrations in early pregnancy and risk of SGA.

Description of Included Studies

Randomized Controlled Trials

Three RCTs were identified for the current report that reported the effects of maternal n-3 supplementation on SGA/IUGR outcomes: one from the POSGRAD trial,³³ one from the DOMInO trial,^{34, 49} and the third by Harper et al.⁴³ Details of these three studies have been described above.

DHA

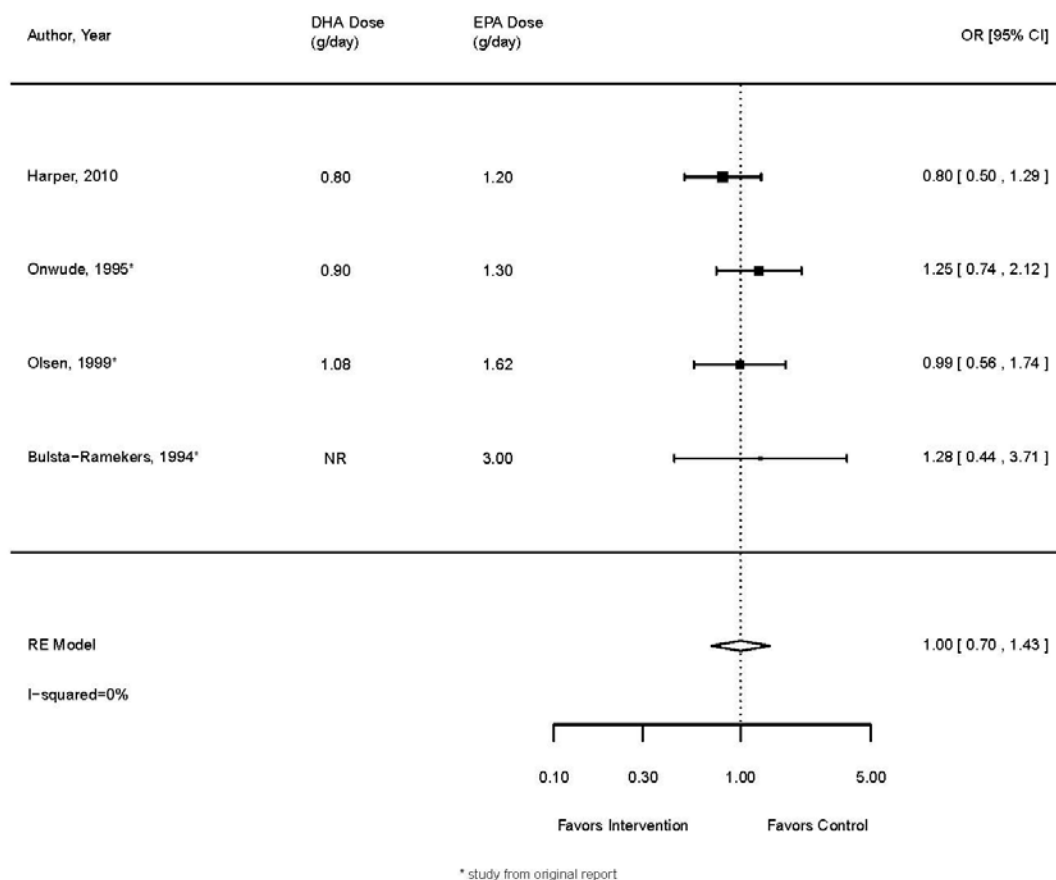
In the POSGRAD trial, Stein et al (2011) reported SGA/IUGR outcomes on the subset of infants who were followed up at 18 months. Among these, 369 pregnant women were randomized to receive 400 mg/day DHA, and 368 were randomized to receive placebo.³³ The authors reported no significant difference in percent of infants born with IUGR between the two groups (10.6 percent DHA vs. 10.3 percent placebo, p=0.91).

Zhou et al (2012) reported SGA/IUGR outcomes among women enrolled in the DOMInO trial.⁴⁹ They found no difference in percent of infants born SGA between the two groups (6.1 percent DHA-enriched fish oil vs. 6.8 percent placebo, p=0.49).

EPA+DHA

In the U.S. study by Harper et al (2010),⁴³ there was also no significant difference in infants born SGA between the progesterone group and the progesterone plus marine oils group. Random effects meta-analysis of the four RCTs enrolling women at risk of SGA/IUGR (this study plus the three from the original report) found no significant effects of DHA+EPA supplementation (doses ranged from 2.0 to 3 g/d) on the incidence of SGA/IUGR between DHA+EPA supplementation and control groups (OR [95% CI]=1.00, CI[0.70, 1.43], $I^2=0\%$) (Figure 12).

Figure 12. SGA – DHA + EPA



Observational studies

Two prospective studies evaluated the association between some measure of maternal n-3 FA exposure and risk of SGA. One⁴⁵ measured dietary n-3 FA intake and the other⁷⁸ measured concentrations of DHA and EPA in the plasma.

n-3 FA Intake

Oken et al.⁴⁵ evaluated the association between maternal n-3 FA intake and risk of having an SGA birth among 2,109 women enrolled in Project Viva, a prospective, observational cohort study of gestational diet, pregnancy outcomes, and offspring health in the U.S. (Massachusetts). The investigators reported no association between quartiles of DHA+EPA intake and risk of having an SGA birth outcome.

n-3 FA Biomarkers

Smits et al.⁷⁸ evaluated the role of plasma DHA and EPA concentrations in the relationship between interpregnancy interval and adverse pregnancy outcome in a subsample (n=1,659) of the Amsterdam Born Children and their Development (ABCD) cohort, a population-based cohort study of multiparous pregnant women in the Netherlands. Women in the lowest quintile of EPA concentration (<0.33 mg/L) in early pregnancy had a two-fold increased risk (OR=2.09, 95% CI 1.32-3.30) of having an SGA birth compared to those in the middle quintile (0.46 -0.58 mg/L). Concentrations of DHA in early pregnancy showed no association with risk of SGA.

Table 5. RCTs for Infants born small gestational age

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Zhou et al., 2012⁴⁹</p> <p>Study name: DOMInO</p> <p>Study dates: 10. 2005 - 01. 2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up article(s)^{34, 48, 50, 51, 52, 53, 3}</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 2399</p> <p>Race of Mother: White European (88%;88%) Asian (7%;8%) Inuit Eskimo (2%;1%) Other race/ethnicity (NR)</p>	<p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: If already taking a dietary supplement containing DHA, their fetus had a known major abnormality, they had a bleeding disorder for which fish oil was contraindicated, they were receiving anticoagulant therapy, they had a documented history of drug or alcohol abuse, they were participating in another fatty acid trial, or English was not the main language spoken at home</p>	<p>Start time: Pregnant medium gestational age 19 weeks</p> <p>Duration: Pregnant birth</p> <p>Arm 1: control Description 500-mg vegetable oil capsules Dose 3*500mg 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Blinding All capsules were similar in size, shape, and color</p> <p>Arm 2: DHA Description DHA-rich fish oil Manufacturer Incromega 500 TG; Croda Chemicals Dose 3*500mg capsule DHA 800 mg EPA 100 mg</p>	<p>Outcome SGA for weight Follow-up time birth Arm 1 82/1202 (6.83%) Arm 2 73/1197 (6.13%)</p>
<p>Hauner et al., 2012³⁶</p> <p>Study name: INFAT</p> <p>Study dates: july 14 2006 - may 22 2009</p> <p>Study design: Trial randomized parallel</p> <p>Location: Germany</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up article(s)^{69, 70, 71}</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 208 Pregnant withdrawals 38 Pregnant completers 170</p> <p>Infants enrolled 188 Infants withdrawals 18 Infants completers 170</p> <p>Pregnant age: 31.9 (4.9) 18-43</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: healthy pregnant women before the 15th wk of gestation, between 18 and 43 y of age, prepregnancy BMI (in kg/m²) between 18 and 30, willingness to implement the dietary recommendations, sufficient German language skills.</p> <p>Exclusion Criteria: high-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity .4); hypertension; chronic diseases (eg, diabetes)</p>	<p>Start time: Pregnant 15th wk of gestation</p> <p>Duration: Pregnant to 4 mo postpartum</p> <p>Arm 1: Control Description brief semistructured counseling on a healthy balanced diet according to the guidelines of the German Nutrition Society and were explicitly asked to refrain from taking fish oil or DHA supplements N-3 Composition. N-6 N-3 2.80 +- 1.17 (SD) at 32nd wk of gestation AA 10.15 +- 3.89 SD) at 32nd wk of gestation</p> <p>Arm 2: Intervention Description Fish-oil supplement + nutritional counseling (to normalize the consumption of AA Brand name Marinol D-40 Manufacturer Lipid Nutrition DHA 1020 mg</p>	<p>Outcome incidence of premature birth Follow-up time birth Arm 1 4/96 (4.2%) Arm 2 3/92 (3.3%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		or gastrointestinal disorders accompanied by maldigestion, malabsorption, or elevated energy and nutritional requirements (e.g., gluten enteropathy); known metabolic defects (eg, phenylketonuria); psychiatric diseases; hyperemesis gravidarum; supplementation with n-3 LCPUFAs before randomization; and alcohol abuse and smoking.	EPA 180 mg N-6 N-3 1.54 +- 0.63 (SD) at 32nd wk of gestation AA 8.82 +- 2.84 (SD) at 32nd wk of gestation Other comment 1 Vit E 9 mg	
<p>Harper et al., 2010⁴³</p> <p>Study name: NR</p> <p>Study dates: 01. 2005 - 10. 2006</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up article(s) ⁴⁷</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 852 Pregnant withdrawals 0 Pregnant completers 852</p> <p>Pregnant age: n3: 28 placebo 27 n3 23-32; placebo 24-32</p> <p>Race of Mother: White European (n3: 56.5; placebo 57.7) Black (n3: 34.1; placebo 34.9) Asian (n3: 3, placebo 1.2) Hispanic (n3: 14.7; placebo 13.6) Other race/ethnicity (NR)</p>	<p>Inclusion Criteria: a documented history of at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation</p> <p>Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug</p>	<p>Start time: Pregnant 16-22 week gestation age</p> <p>Duration: Pregnant 36 weeks of gestation</p> <p>Arm 1: placebo Description inert mineral oil Manufacturer Eminent Services, Frederick, MD Active ingredients 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose four capsules of matching oil containing a minute amount of inert mineral oil Blinding Boxes containing a woman's entire supply of capsules in blister packs were sequentially numbered according to the predetermined randomization sequence, and on enrollment a woman was assigned the next number in sequence. Study group assignment was not known by study participants, their health care providers, or the research personnel</p> <p>Arm 2: Eminent Services, Frederick, MD Active ingredients 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose in 4 capsules total 2000 mg of n3 DHA 800 mg</p>	<p>Outcome SGA less than 10th percentile</p> <p>Follow-up time birth</p> <p>Arm 1 41/410 (10%)</p> <p>Arm 2 35/427 (8.2%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	EPA 1200 mg	
<p>Stein et al., 2011³³</p> <p>Study name: NR</p> <p>Study dates: 02. 2005-02.2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: Mexico</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 1094 Pregnant completers 973</p> <p>Pregnant age: placebo 26.3; DHA 26.4 (placebo 4.6; DHA 4.9)</p> <p>Infant age: 39.1 (placebo 1.6; DHA 1.8)</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breast-feed for at least 3 mo, and to live in the area for at least 2 y after delivery</p> <p>Exclusion Criteria: NR</p>	<p>Start time: Pregnant 18-22 Gestinal week Infants birth</p> <p>Duration: Pregnant birth</p> <p>Arm 1: Placebo Description Olive oil Manufacturer Martek Biosciences Dose 2 capsules olive oil Blinding Similar in appearance and taste to DHA capsules</p> <p>Arm 2: DHA Description algal DHA capsules Manufacturer Martek Biosciences Dose 2 capsules * 200mg DHA 400 mg</p>	<p>Outcome IUGR (intrauterine growth retardation); birth weight for gestational age < 10th percentile</p> <p>Follow-up time birth</p> <p>Arm 1 38/368 (10.3%)</p> <p>Arm 2 39/369 (10.6%)</p>

Table 6. Observational studies for Infants born small gestational age

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Muthayya, et al., 2009⁷⁷</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: NR</p> <p>Funding source / conflict: Industry, Government</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 829 Pregnant completers 676</p> <p>Pregnant age: group 1, 23 group 2, 23 group 3, 23 total, 24 group 1, 21-26 group 2, 21-27 group 3, 23-29 total: 21-27</p> <p>Race of Mother: Asian (Indian, 100%)</p>	<p>Inclusion Criteria: regnant women aged 17–40 years and at <20 weeks of gestation, registered for antenatal screening at the Department of Obstetrics and Gynecology at St John's Medical College Hospital,</p> <p>Exclusion Criteria: Women with multiple pregnancies, those with a clinical diagnosis of chronic illness such as diabetes mellitus, hypertension, heart disease and thyroid disease, those who tested positive for HbSAg/HIV/VDRL infection or who anticipated moving out of the city before delivery were excluded</p>
<p>Smits, et al., 2013⁷⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: None</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 1659 Pregnant completers 1659</p> <p>Infants enrolled 1659 Infants completers 1659</p> <p>Pregnant age: <25 y, 5.7% 25-34 y, 61.2% ≥35 y, 33.1%</p> <p>Infant age: 40.0 weeks (1.2)</p> <p>Race of Mother: White European (88.4)</p>	<p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: primiparous women or delivered preterm</p>

Birth Weight

Key Findings and Strength of Evidence for Birth Weight

- Pooled analysis of 11 RCTs showed significantly higher birth weights among infants whose mothers received algal DHA or DHA-enriched fish oil compared to placebo (WMD [95% CI]=103.13 [6.83 199.43] grams).
- Pooled analysis of 5 RCTs found no effect of maternal EPA+DHA supplementation on infant birth weight.
- One RCT assessing the effects of ALA on infant birth weight showed no effects.
- Two prospective observational studies showed no association between maternal n-3 FA intake from supplements and infant birth weight.
- Three prospective observational studies assessing the effects of maternal dietary n-3 FA intake on infant birth weight showed inconsistent results. Two studies found no association between dietary n-3 FA intake and infant birth weight. The third study found that infants born to mothers in the lowest quartile of DHA+EPA intake had significantly higher birth weights than infants born to mothers in the highest quartile of DHA+EPA intake. This association held true for DHA+EPA intake measured in all three trimesters of pregnancy.
- Three prospective observational studies showed that maternal n-3 FA biomarker levels were significantly and positively associated with infant birth weight.

Description of Included Studies

The original report included 12 RCTs (in 9 publications) that compared mean birth weight values (in grams) between maternal n-3 FA supplemented and control groups. Of these studies, pregnant women received DHA-enriched eggs (DHA 0.23 g/d) in two RCTs, fish oil supplements (EPA+DHA doses ranged from 0.23 to 5 g/d) in nine RCTs, and dietary supplementation with margarine delivering ALA (2.82 g/d) and linoleic acids (9.02 g/d) in one RCT. The between-group difference in the mean birth weight was not significantly different in eight of the 12 studies, was significantly higher in the n-3 FA supplementation groups compared with controls in three studies (1 DHA-enriched eggs, 1 fish oil supplementation, and 1 dietary supplementation with ALA and linoleic acids), and was significantly lower in the fish oil supplementation (EPA+DHA 2.2 g/d) than in the control group (olive oil) in one study. Only one prospective cohort study was included in the original report. This cohort study found that the maternal plasma triglyceride AA, but not phospholipid or cholesteryl ester AA, was positively related to infant birth weight and length ($p<0.01$). No other correlations were found between maternal plasma n-3 or n-6 FA and these variables.

Sixteen new RCTs and eight observational studies were identified for the current report. All studies were conducted among healthy, pregnant women and followed up until birth. Overall we found a moderate level of evidence that maternal supplementation of DHA or DHA-rich fish oils may increase birth weight but the minimal DHA dose threshold for the effect is still unclear. This finding is consistent with findings from the observational studies, which found that higher maternal blood DHA concentrations were associated with higher birth weight.

Randomized Controlled Trials

Sixteen unique RCTs were identified for the current report. Of these, three RCTs (in 5 publications) compared algal DHA supplements with placebo controls,^{30-33, 79} eight (in nine publications) compared DHA-rich fish oil supplementation (DHA:EPA ratio $\geq 5:1$) with placebo controls,^{34, 36-41, 49, 64} five compared fish oil supplements (EPA+DHA, DHA:EPA ratio $<5:1$) with placebo,^{41-43, 80, 81} and one compared black current seed oil (ALA 0.42 g/d; 0.09 SDA g/d) with placebo.⁸² Of these, one RCT compared both DHA-rich fish oil supplement and fish oil supplement, with placebo.⁴¹

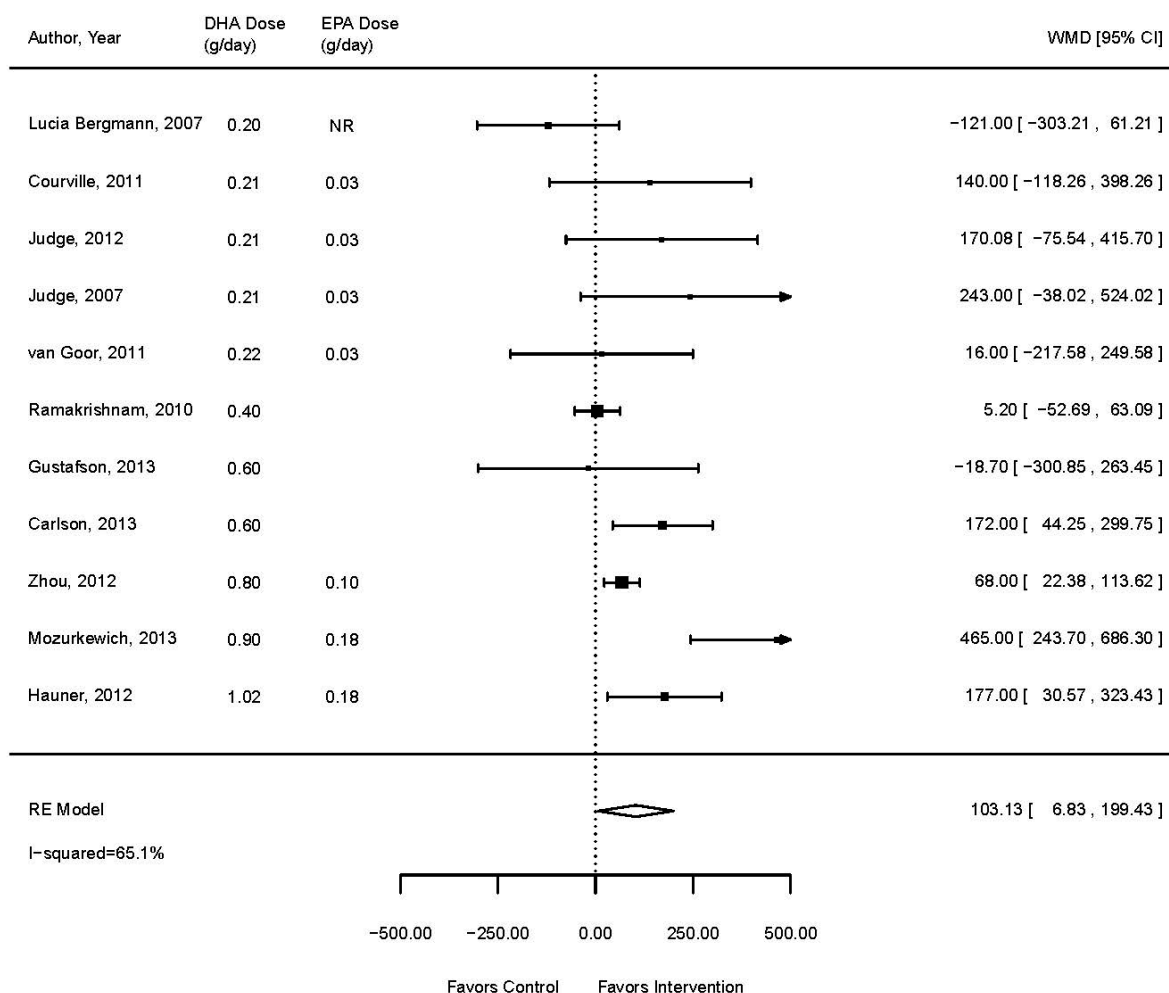
DHA

Three RCTs (in five publications) randomized healthy pregnant women between 12 and 20 weeks of gestation to DHA supplements from algae oil (0.4 or 0.6 g/d DHA) or placebo (soybean, corn, or olive oil).^{30-33, 79} Two RCTs analyzed the birth weight outcome in a total of 353 mothers and their infants living in the U.S.,^{30, 79} and one analyzed 973 mothers and their infants in Mexico (POSGRAD trial).³¹⁻³³ It should be noted that, of the three publications from the POSGRAD trial, the Ramakrishnan et al. (2010) publication analyzed the largest number of study participants,³¹ while the other two publications analyzed a subset of the trial participants.^{32, 33} Thus, only results from Ramakrishnan et al. (2010) were included in our meta-analysis. Overall, only one of the three RCTs found a significantly higher mean birth weight (+172 grams, $P=0.004$) in infants whose mothers received DHA (0.6 g/d) supplementation ($n=154$) than those whose mothers received placebo ($n=147$).³⁰ The other two RCTs (DHA 0.4 and 0.6 g/d) did not find significant differences in mean birth weight between DHA supplementation and placebo groups.^{31-33, 79}

Eight RCTs randomized healthy pregnant women between 12 and 24 weeks of gestation to DHA-rich fish oil supplementation or controls. Studies were conducted in the U.S. ($n=4$), Germany ($n=2$), Australia ($n=1$), and the Netherlands ($n=1$). Of the eight RCTs, three compared DHA-containing cereal-based bars (mean DHA 0.214-0.240 and EPA 0.027-0.030 g/d; DHA:EPA ratio = 8) with placebo bars;³⁷⁻³⁹ four (in five publications) compared DHA-rich fish oil supplements (DHA 0.200-1.020 and EPA 0.100-0.180 g/d; DHA:EPA ratio = 5-8),^{36, 40, 41} with controls (vegetable oil, nutritional counseling, vitamins and minerals, or soy oil), and one is a three-arm RCT compared DHA-rich fish oil plus soybean oil (DHA 0.220 and EPA 0.036 g/d plus ALA 0.032 g/d), DHA-rich fish oil plus AA (DHA 0.220 and EPA 0.036 g/d plus AA 0.220 g/d) with placebo (soybean oil).⁶⁴ Five of the eight RCTs with lower DHA doses (0.2-0.22 g/d) did not find significant difference in the mean birth weight between DHA supplementation and placebo in a total of 316 infants,^{37-40, 64} while the other three RCTs (in four publications) with higher DHA doses (0.8-1.02 g/d) all found a significantly higher mean birth weight in infants whose mothers received DHA-rich fish oil supplement compared with those whose mothers received placebo (+68 to +465 grams) in a total of 2,656 infants.^{34, 36, 41, 49} The three-arm RCT also did not find a significant difference in the mean birth weight between DHA-rich fish oil plus AA (DHA 0.220 and EPA 0.036 g/d plus AA 0.220 g/d, $n=39$) compared with placebo (soybean oil, $n=34$).⁶⁴

Our random-effects meta-analysis of 11 RCTs showed that the mean birth weight was significantly higher in infants whose mothers received algal DHA or DHA-rich fish oil supplement compared with those whose mothers received placebo (WMD [95% CI]=103.13 [6.83 199.43] grams), with high heterogeneity ($I^2 = 65.1$). (Figure 13)

Figure 13. Birth Weight (g) - DHA vs Placebo



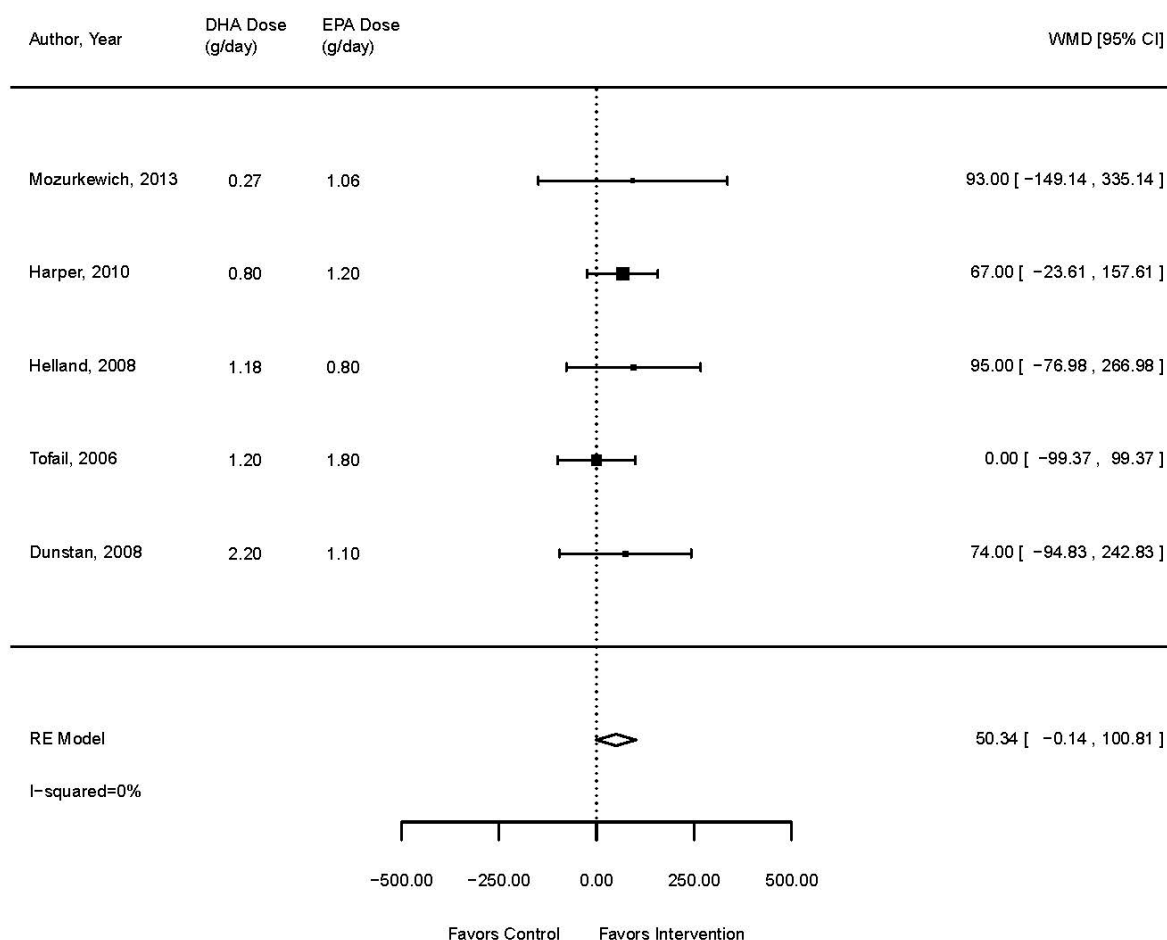
EPA+DHA

Five RCTs randomized healthy pregnant women between 12 and 25 weeks of gestation to fish oil supplements (EPA+DHA) or placebo (soybean oil, corn oil, olive oil or inert mineral oil).^{41-43, 80, 81} Studies were conducted in the U.S. (n=3), Norway (n=1), and Bangladesh (n=1). The doses of EPA ranged from 0.8 to 1.8 g/d, and the doses of DHA ranged from 0.27 to 2.2 g/d. The DHA to EPA ratio ranged from 0.26 to 2. The total doses of EPA plus DHA ranged from 1.3 to 3.3 g/d. None of these studies found a significant difference in mean birth weight between groups.

Our random-effects meta-analysis of five RCTs showed that maternal fish oil supplementation (EPA+DHA doses ranged from 1.3 to 3.3 g/d) did not have a significant effect

on birth weight compared with placebo (WMD [95% CI]=50.34 [-0.14, 100.81]) grams, with no heterogeneity ($I^2 = 0\%$). (Figure 14)

Figure 14. Birth Weight (g) - DHA + EPA vs. placebo



ALA

One RCT randomized healthy pregnant women (<16 weeks of gestation) to either black current seed oil (ALA 0.42 g/d; SDA 0.09 g/d) or placebo (olive oil). The results did not show a significant difference in birth weight between groups in a total of 241 infants.⁸²

Observational studies

Eight prospective cohort studies that assessed the association between n-3 FA intakes or status and birth weight were identified for the current report. Of these, five studies assessed the

associations between maternal dietary intake of n-3 FA (from foods or supplements) and birth weight.^{45, 46, 83-85} The other three studies examined the relationships between maternal n-3 FA biomarkers and birth weight.^{71, 78, 86}

n-3 FA Intake

Two studies assessed the associations between maternal n-3 FA intake from supplements and birth weight.^{84, 85} The Norwegian Mother and Child Cohort Study (MoBa), which enrolled a nation-wide pregnancy cohort, did not find significant associations between maternal supplementary n-3 FA intake (g/d) at 28 weeks of gestation and infants' birth weight (n=61,387). In contrast, a small cohort study in Iceland found that infants born to mothers who reported taking liquid cod liver oil in first trimester had higher birth weight (132 [95% CI 18, 246] grams) compared with those born to mothers who did not take liquid cod liver oil in first trimester (n=350).

Three studies assessed the associations between maternal dietary n-3 FA intake and birth weight.^{45, 46, 83} Two of the three studies, in a total of 1816 mother-infant pairs, did not find a significant association between maternal dietary n-3 FA intake and birth weight.^{46, 83} The third study, by Oken et al.,⁴⁵ evaluated the association between quartiles of maternal DHA+EPA intake (median 0.02 g/d) and birth weight: They found that infants born to mothers in the lowest quartile of DHA+EPA intake had higher birth weight than those born to mothers in the highest quartile of DHA+EPA intake (median 0.27 to 0.38 g/d) during the first (94 [95%CI 23, 166] grams, n=1797), second (50 [95%CI -19, 119] grams, n=1663), and third (90 [95%CI 33, 147] grams, n=2070) trimesters.

n-3 FA Biomarkers

Three prospective cohort studies examined the relationships between maternal n-3 FA biomarkers and birth weight.^{71, 78, 86} All three studies assessed blood DHA measures (one RBC; two plasma phospholipids). One study each also assessed RBC total n-3 FA⁷¹ and plasma EPA.⁷⁸ All three studies found that higher maternal blood DHA concentrations were associated with higher birth weight. Similar findings were reported for the associations between plasma EPA or RBC total n-3 FA concentrations and birth weight. Individual study findings are described below.

The INFAT study,⁷¹ conducted in Germany, enrolled healthy pregnant women at the 14th week of gestation and examined the associations between maternal RBC DHA and total n-3 FA at 32 weeks of gestation and birth weight. They found that per unit increase in percent maternal RBC DHA or percent total n-3 FA of total FA were significantly associated with an average of 24 (95% CI 0.42, 48) and 20 (95% CI 2.78, 38) grams increase in birth weight (n=187).

Dirix et al., 2009⁸⁶ enrolled healthy pregnant women less than 16 weeks of gestation and measured their plasma DHA (% w/w plasma phospholipids) at 16, 22, and 32 weeks of gestation. This study found that per unit increase in maternal plasma DHA content (% w/w plasma phospholipids) at 16 weeks of gestation was significantly associated with an average of 52 (95% CI 20, 84) grams increase in infants' birth weight (n=665). Per unit increase in maternal plasma DHA content (% w/w plasma phospholipids) at 22 weeks (n=623) and 32 weeks (n=644) of gestation were marginally associated with an average of 31 (95% CI -4.3, 67) and 33 (95% CI -5.7, 72) grams increase in infants' birth weight, respectively.

Smits et al.⁷⁸ analyzed the associations between plasma DHA and EPA concentrations and infants' birth weight in a subsample (n=1,659) of the Amsterdam Born Children and their Development (ABCD) cohort, a population-based cohort study of multiparous pregnant women

in the Netherlands. Infants born to mothers in the lowest quintile of EPA concentration (<0.33 mg/L) or DHA concentration (<3.74 mg/L) in early pregnancy had significantly lower birth weight (-182.5 [39 SE] or -118.2 [39 SE] grams, respectively) compared with those born to mothers in the middle quintile (EPA $0.46 - 0.58$ mg/L or DHA $4.35 - 4.86$ mg/L).

Table 7. RCTs for Birth Weight

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Makrides et al., 2010³⁴</p> <p>Study name: DOMInO</p> <p>Study dates: 2005-2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up article(s) ^{48, 49, 50, 51, 52, 53, 3}</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 2399 Pregnant withdrawals 1</p> <p>Infants enrolled 605 Infants withdrawals 32 Infants completers 726</p> <p>Pregnant age: 28.9 (DHA5.7; control5.6)</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: with singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments</p> <p>Exclusion Criteria: already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home</p>	<p>Start time: Pregnant < 21 week's gestation</p> <p>Duration: NR</p> <p>Arm 1: vegetable oil capsules Description a blend of 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Manufacturer Efamol, Surrey, England. Dose 3* 500mg capsule / day Blinding All capsules were similar in size, shape, and color</p> <p>Arm 2: DHA Description DHA-rich fish oil concentrate Manufacturer ; Incromega 500 TG, Croda Chemicals, East Yorkshire, England Dose 500mg capsule *3/day DHA 800mg EPA 100mg</p>	<p>duplicate data of id 4404</p>
<p>Zhou et al., 2012⁴⁹</p> <p>Study name: DOMInO</p> <p>Study dates: 10. 2005 - 01. 2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 2399</p> <p>Race of Mother: White European (88%;88%) Asian (7%;8%) Inuit Eskimo (2%;1%) Other race/ethnicity (NR)</p>	<p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: If already taking a dietary supplement containing DHA, their fetus had a known major abnormality, they had a bleeding disorder for which fish oil was contraindicated, they were receiving</p>	<p>Start time: Pregnant medium gestationl age 19 weeks</p> <p>Duration: Pregnant birth</p> <p>Arm 1: control Description 500-mg vegetable oil capsules Dose 3*500mg 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Blinding All capsules were similar in size, shape, and color</p>	<p>Outcome birth weight Follow-up time birth Arm 1 Sample size 1202 mean 3407 SD (576) Arm 2 Sample size 1197 mean 3475 SD (564)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up article(s) ^{34, 48, 50, 51, 52, 53, 3}</p>		<p>anticoagulant therapy, they had a documented history of drug or alcohol abuse, they were participating in another fatty acid trial, or English was not the main language spoken at home</p>	<p>Arm 2: DHA Description DHA-rich fish oil Manufacturer Incromega 500 TG; Croda Chemicals Dose 3*500mg capsule DHA 800 mg EPA 100 mg</p>	
<p>Dunstan et al., 2008⁴²</p> <p>Study name: Dunstan</p> <p>Study dates: 2000-2003</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: NR</p> <p>Follow-up article(s) ^{56, 57, 58, 59}</p>	<p>Study Population: Healthy infants Pregnant women with allergies</p> <p>Pregnant enrolled 98 Pregnant completers 83</p> <p>Infants enrolled 83 Infants withdrawals 11 (7 FO, 4 control) Infants completers 72</p> <p>Pregnant age: Fish oil: 30.9 Control: 32.6 (Fish oil: 3.7 Control: 3.6)</p> <p>Infant age: Term (mean gestational period 275 days)</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: Healthy term infants of pregnant women enrolled in RCT of gestational supplementation</p> <p>Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected</p>	<p>Start time: Pregnant 20 weeks gestation</p> <p>Duration: Pregnant to term</p> <p>Arm 1: Control Description olive oil placebo Blinding capsules image matched Maternal conditions Current smoker 0% Maternal allergies 100%</p> <p>Arm 2: Fish oil Description same Manufacturer Ocean Nutrition, Halifax Nova Scotia Active ingredients 3-4mg/g vitamin E Viability none reported Dose 4 1-gm capsules fish oil per day Maternal conditions DHA 2.2 EPA 1.1 Current smoker 0% Maternal allergies 100% Other comment 1 fish oil supplying 2,2g/d DHA and 1.1g/day EPA</p>	<p>Outcome birth weight Follow-up time birth Arm 1 Sample size 39 mean 3434 SD (377) Arm 2 Sample size 33 mean 3508 SD (353)</p>
<p>Goor et al., 2011⁶⁴</p> <p>Study name: Groningen LCPUFA study</p> <p>Study dates: 2004-2009</p> <p>Study design: Trial</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 119</p> <p>Infants enrolled 119 Infants completers 114</p>	<p>Inclusion Criteria: women with a first or second low-risk singleton pregnancy, between the 14th and 20th weeks of pregnancy</p> <p>Exclusion Criteria:</p>	<p>Start time: Pregnant 14th-20th week pregnancy Lactating 3 months after delivery Mothers 3 months after delivery Infants NR</p> <p>Duration: Pregnant NR Lactating 33-39 weeks Mothers 33-39 weeks Infants NR</p> <p>Arm 1: placebo</p>	<p>Outcome birth weight Follow-up time birth Arm 1 Sample size 34 mean 3576 SD (551) Arm 2 Sample size 41 mean 3592 SD (465) Arm 3 Sample size 39 mean 3652 SD (377)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>randomized parallel</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 18 months (multiple IDs)</p> <p>Follow-up article(s) ^{61, 62, 63, 65, 66, 67, 68, 35}</p>	<p>Pregnant age: Placebo: 32.7 DHA: 32.5 DHA+AA: 32.9 (Placebo: 5.1 DHA: 4.4 DHA+AA: 4.8)</p> <p>Infant age: 18 months</p> <p>Race of Mother: NR (100)</p>	<p>women with vegetarian or vegan diets; women with diabetes mellitus; birth complications</p>	<p>Description Soy bean oil</p> <p>Brand name none</p> <p>Arm 2: DHA</p> <p>Description DHA plus soy bean oil</p> <p>Brand name Marinol D40</p> <p>Manufacturer Lipid Nutrition B.V., Wormerveer, The Netherlands; AA:</p> <p>Dose 1 capsule DHA and 1 capsule soy bean oil once a day</p> <p>ALA 32 mg/d</p> <p>DHA 220 mg/d</p> <p>EPA 34 mg/d</p> <p>Arm 3: DHA+AA</p> <p>Description DHA plus AA</p> <p>Brand name AA: no brand name</p> <p>Manufacturer Wuhan Alking Bioengineering Co. Ltd., Wuhan, China</p> <p>Dose 2 capsules once a day</p> <p>ALA 7 mg/d</p> <p>DHA 220 mg/d</p> <p>EPA 36 mg/d</p> <p>AA 220 mg per capsule</p>	
<p>Hauner et al., 2012³⁶</p> <p>Study name: INFAT</p> <p>Study dates: july 14 2006 - may 22 2009</p> <p>Study design: Trial randomized parallel</p> <p>Location: Germany</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up article(s) ^{69, 70, 71}</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 208 Pregnant withdrawals 38 Pregnant completers 170</p> <p>Infants enrolled 188 Infants withdrawals 18 Infants completers 170</p> <p>Pregnant age: 31.9 (4.9) 18-43</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: healthy pregnant women before the 15th wk of gestation, between 18 and 43 y of age, prepregnancy BMI (in kg/m²) between 18 and 30, willingness to implement the dietary recommendations, sufficient German language skills.</p> <p>Exclusion Criteria: high-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity .4); hypertension; chronic diseases (eg, diabetes) or gastrointestinal disorders accompanied</p>	<p>Start time: Pregnant 15th wk of gestation</p> <p>Duration: Pregnant to 4 mo postpartum</p> <p>Arm 1: Control</p> <p>Description brief semistructured counseling on a healthy balanced diet according to the guidelines of the German Nutrition Society and were explicitly asked to refrain from taking fish oil or DHA supplements</p> <p>N-3 Composition.</p> <p>N-6 N-3 2.80 +- 1.17 (SD) at 32nd wk of gestation</p> <p>AA 10.15 +- 3.89 SD) at 32nd wk of gestation</p> <p>Arm 2: Intervention</p> <p>Description Fish-oil supplement + nutritional counseling (to normalize the consumption of AA</p> <p>Brand name Marinol D-40</p> <p>Manufacturer Lipid Nutrition</p> <p>DHA 1020 mg</p> <p>EPA 180 mg</p> <p>N-6 N-3 1.54 +- 0.63 (SD) at 32nd wk of gestation</p>	<p>Outcome birth weight</p> <p>Follow-up time birth</p> <p>Arm 1 Sample size 96 mean 3357 SD (557)</p> <p>Arm 2 Sample size 92 mean 3534 SD (465)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		by maldigestion, malabsorption, or elevated energy and nutritional requirements (e.g., gluten enteropathy); known metabolic defects (eg, phenylketonuria); psychiatric diseases; hyperemesis gravidarum; supplementation with n-3 LCPUFAs before randomization; and alcohol abuse and smoking.	AA 8.82 +- 2.84 (SD) at 32nd wk of gestation Other comment 1 Vit E 9 mg	
<p>Carlson et al., 2013³⁰</p> <p>Study name: NR</p> <p>Study dates: 2006.01-2011.10</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 350 Pregnant withdrawals 49 Pregnant completers 301</p> <p>Pregnant age: placebo: 24.8; DHA: 25.3 (placebo 4.7; DHA 4.9)</p> <p>Race of Mother: Black (46%;37%) Non-black (54%; 63%)</p>	<p>Inclusion Criteria: Englishspeaking, between 8 and 20 wk of gestation, between 16 and 35.99 y of age, and planning to deliver at a hospital in the Kansas City metropolitan area</p> <p>Exclusion Criteria: carrying more than one fetus, had preexisting diabetes mellitus or systolic blood pressure \$140 mm Hg at enrollment, or had any serious health condition likely to affect the prenatal or postnatal growth and development of their offspring, including cancer, lupus, hepatitis, HIV/AIDS, or a diagnosed alcohol or chemical dependency. or if the initial screening based on their self-reported weight and</p>	<p>Start time: Pregnant 99.6/102.9 day</p> <p>Duration: Pregnant enrollment to birth</p> <p>Arm 1: Placebo Description half soybean and half coin oil Manufacturer DSM Nutritional Products) Active ingredients a-linolenic acid Dose 3 *capsule 200/day Blinding both DHA and placebo capsules were orange flavored</p> <p>Arm 2: DHA Description marine algae-oil source of DHA Manufacturer DHASCO; DSM Nutritional Products, formerly Martek Biosciences) Dose 200 mg capsule, 3 times a day DHA 200mg/capsule * 3</p>	<p>Outcome birth weight Follow-up time birth Arm 1 Sample size 147 mean 3187 SD (602) Arm 2 Sample size 154 mean 3359 SD (524)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		height suggested a BMI (in kg/m ² >=40).		
<p>Courville et al., 2011³⁷</p> <p>Study name: NR</p> <p>Study dates: nr</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry, Government</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 47 Pregnant withdrawals 0 Pregnant completers 47</p> <p>Pregnant age: NR (NR) NR</p> <p>Race of Mother: White European (8.5) Black (10.6) Asian (4.3) Minority (Puerto Rican/Latino 66%; Afriecan - other 8.5%; Other or mixed ethnicity = 2%)</p>	<p>Inclusion Criteria: Healthy pregnant women, mid-pregnancy (20–24 weeks)</p> <p>Exclusion Criteria: parity .5; history of chronic hypertension; hyperlipidaemia; renal or liver disease; heart disease; thyroid disorder; multiple gestations; having been pregnant or lactating in the previous 2 years.</p>	<p>Start time: Pregnant 20-24 wk of gestation</p> <p>Duration: Pregnant until birth</p> <p>Arm 1: Placebo Description placebo bars (Manufacturer Nestec Limited (Vevey, Switzerland) Dose 5 placebo bars per week Blinding NR</p> <p>Arm 2: DHA-FF Description DHA cereal-based bars Manufacturer Nestec Limited (Vevey, Switzerland) Dose 5DHA cereal-based bars per week DHA 241 mg/d EPA 30.1 mg/d</p>	<p>Outcome birth weight Follow-up time birth</p> <p>Arm 1 Sample size 25 mean 3.19 SD (0.44)</p> <p>Arm 2 Sample size 22 mean 3.33 SD (0.46)</p>
<p>Gustafson et al., 2013⁷⁹</p> <p>Study name: NR</p> <p>Study dates: may 2009 - july 2011</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 67 Pregnant withdrawals 12 Pregnant completers 52</p> <p>Infants enrolled 44 Infants completers 41</p> <p>Pregnant age: placebo 25.6+; DHA 25.5 (placebo 4.8; DHA 4.3)</p> <p>Race of Mother: White European (46.3) Black (37.3) Asian (3) Hispanic (13.4)</p>	<p>Inclusion Criteria: between 16–35.9 years of age and carrying a singleton pregnancy between the 12th and 20th week of gestation</p> <p>Exclusion Criteria: any serious health condition likely to affect the growth and development of the fetus or health of the mother including cancer, lupus, hepatitis, diabetes mellitus (Type1, Type 2 or gestational) or HIV/AIDS at baseline or fetal cardiac structural or conduction defects. Women who self-reported illicit drug use or alcohol use during</p>	<p>Start time: Pregnant 12-20 week gestation Infants birth</p> <p>Duration: Pregnant till birth</p> <p>Arm 1: Placebo Description g 50% soy and 50% corn oil Manufacturer Martek Biosciences, now DSM Nutritional Products Dose 3 capsule a day each 500 mg Blinding Only members of the investigational pharmacy knew the subject allocation. Participants and all members of the investigational team were blinded to the intervention assignment. Participants were allocated to either group based on the simple randomization procedure using random numbers generated by SAS. All capsules were the same color, size, weight and the oils were orange-flavored to prevent investigator or subject bias.</p> <p>Arm 2: algal oil as a source of DHA (200 mg of DHA per capsule for a total of 600 mg DHA/day) Dose 3 capsule of 200mg DHA total 600 mg</p>	<p>Outcome birth weight Follow-up time birth</p> <p>Arm 1 Sample size 24 mean 3435.5 SD (404.8)</p> <p>Arm 2 Sample size 22 mean 3416.8 SD (552.9)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		pregnancy and those with hypertension or BMI Z40 were excluded. Women who were taking more than 200 mg/day DHA in prenatal vitamins or over the counter supplements were excluded from participation	DHA 200 mg * 3	
<p>Harper et al., 2010⁴³</p> <p>Study name: NR</p> <p>Study dates: 01. 2005 - 10. 2006</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up article(s) ⁴⁷</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 852 Pregnant withdrawals 0 Pregnant completers 852</p> <p>Pregnant age: n3: 28 placebo 27 n3 23-32; placebo 24-32</p> <p>Race of Mother: White European (n3: 56.5; placebo 57.7) Black (n3: 34.1; placebo 34.9) Asian (n3: 3, placebo 1.2) Hispanic (n3: 14.7; placebo 13.6) Other race/ethnicity (NR)</p>	<p>Inclusion Criteria: a documented history of at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation</p> <p>Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37</p>	<p>Start time: Pregnant 16-22 week gestation age</p> <p>Duration: Pregnant 36 weeks of gestation</p> <p>Arm 1: placebo Description inert mineral oil Manufacturer Eminent Services, Frederick, MD Active ingredients 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose four capsules of matching oil containing a minute amount of inert mineral oil Blinding Boxes containing a woman's entire supply of capsules in blister packs were sequentially numbered according to the predetermined randomization sequence, and on enrollment a woman was assigned the next number in sequence. Study group assignment was not known by study participants, their health care providers, or the research personnel</p> <p>Arm 2: Eminent Services, Frederick, MD Active ingredients 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose in 4 capsules total 2000 mg of n3 DHA 800 mg EPA 1200 mg</p>	<p>Outcome birth weight Follow-up time birth Arm 1 Sample size 418 median 2923 IQR (2389, 3317) Arm 2 Sample size 434 median 2990 IQR (2585, 3330) Outcome birthweight <2500g Follow-up time birth Arm 1 112/410 (27.3%) Arm 2 94/427 (22%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		weeks of gestation		
<p>Helland et al., 2008⁸⁰</p> <p>Study name: NR</p> <p>Study dates: 1994-2003</p> <p>Study design: Trial randomized parallel</p> <p>Location: Norway</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: 7 years 6729, 10331: both in original report; and 10608 (biomarkers)</p> <p>Follow-up article(s) ^{52, 87, 88}</p>	<p>Study Population: Healthy infants Healthy pregnant women Breast-feeding women</p> <p>Infants enrolled 262 Infants completers 143</p> <p>Pregnant age: cod oil 28.6 n=175 corn oil 27.6 n=166 (cod oil 3.4; corn oil 3.2)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Healthy nulliparous or primiparous women, aged 19-35 with single pregnancies</p> <p>Exclusion Criteria: Unhealthy neonates</p>	<p>Start time: Pregnant week 18 of pregnancy</p> <p>Duration: NR</p> <p>Arm 1: Cod oil Manufacturer Peter Moller, Avd Orkla ASA, Oslo, Norway Active ingredients Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively N-3 Composition. DHA 1183mg/10 mL EPA 803 mg/10mL Total N-3 2494 mg/10mL</p> <p>Arm 2: corn oil Active ingredients Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively ALA 92 mg/10mL</p>	<p>Outcome birth weight</p> <p>Follow-up time birth</p> <p>Arm 1 Sample size 61 mean 3518 SD (560)</p> <p>Arm 2 Sample size 82 mean 3613 SD (458)</p>
<p>Judge et al., 2007³⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict:</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 29 Pregnant completers 29</p> <p>Pregnant age: 23.75 years (.4 years) NR</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: women aged 18 –35 y who were at 20 wk of gestation</p> <p>Exclusion Criteria: Women with a history of drug or alcohol addiction, hypertension, smoking, hyperlipidemia, renal disease, liver disease, diabetes, or psychiatric disorder</p>	<p>Start time: Pregnant 24 weeks gestation</p> <p>Duration: Pregnant until birth</p> <p>Arm 1: placebo Description cereal based placebo bars Manufacturer Nestec? Active ingredients 18 g carbohydrates, 1.3 grams protein, 92 calories, 1.7 g fat Viability NR Dose 5 bars per week Blinding NR</p>	<p>Outcome birth weight</p> <p>Follow-up time birth</p> <p>Arm 1 Sample size 15 mean 3222 SD (363)</p> <p>Arm 2 Sample size 14 mean 3465 SD (406)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Industry, Government, None			<p>Arm 2: DHA supplemented cereal bars Manufacturer Nestec? Active ingredients 18 g carbohydrates, 1.3 grams protein, 92 calories, 1.7 g fat Viability NR Dose 5 bars per week. DHA-containing cerealbased bars [1.7 g total fat, 300 mg DHA as low-eicosapentaenoic oil (EPA) fish oil; EPA:DHA 1:8 per bar DHA mg/d EPA .75 mg (calculated based on EPA:DHA ratio) EPA-DHA 1:8</p>	
<p>Judge et al., 2012³⁹</p> <p>Study name: NR</p> <p>Study dates: nr</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: NR</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 48</p> <p>Pregnant age: Treatment group: 23.93 Placebo: 23.86 (Treatment group: 4.32 Placebo: 4.53)</p> <p>Race of Mother: White European (Treatment: 11.1%, Placebo: 0%) Black (Treatment: 18.5%, Placebo: 4.8%) Asian (Treatment: 3.7%, Placebo: 0%) Hispanic (Treatment: 59.3%, Placebo: 80.9%) NR (Treatment: 7.4%, 3 (14.3%))</p>	<p>Inclusion Criteria: The women were either primiparous or had not been pregnant for the past 2 years.</p> <p>Exclusion Criteria: parity greater than 5, history of chronic hypertension, hyperlipidemia, renal, liver or heart disease, thyroid disorder, multiple gestations or pregnancy induced complications including hypertension, preeclampsia or preterm labor, smoking and psychiatric disorders. Women who were treated during labor with analgesics such as Stadol (butorphanol tartrate), that may cause infant respiratory distress were also excluded. In addition, infants born preterm and infants with less than 4 h of crib time in the first and second days postpartum were excluded from the</p>	<p>Start time: Pregnant 24 weeks gestation</p> <p>Duration: Pregnant until delivery</p> <p>Arm 1: Placebo Description Control group Manufacturer estec, S.A., Switzerland Blinding The total macronutrient content was the same in both the DHA and placebo bars with respect to carbohydrate, protein and fat, however, the DHA bars contained fish oil (300 mg DHA) and the placebo bars contained corn oil.</p> <p>Arm 2: DHA Description Intervention group Manufacturer estec, S.A., Switzerland Dose average of 5 bars weekly DHA 300 mg EPA-DHA 8:1 ratio of DHA to EPA</p>	<p>Outcome birth weight</p> <p>Follow-up time birth</p> <p>Arm 1 Sample size 21 mean 3224.62 SD (431.25)</p> <p>Arm 2 Sample size 27 mean 3394.7 SD (430)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		analyses.		
<p>Linnamaa et al., 2010⁸²</p> <p>Study name: NR</p> <p>Study dates: 2004-2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Finland</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Infants enrolled 314 Infants withdrawals 137 Infants completers 177</p> <p>Mother age: NR (NR) NR</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: All pregnant mothers <16 weeks of gestation</p> <p>Exclusion Criteria: Sick children and those born prematurely who required more intensive care (n=8)</p>	<p>Start time: Pregnant 8th to 16th weeks of pregnancy and then continued Infants when exclusive breastfeeding ended</p> <p>Duration: Pregnant until the end of the exclusive breastfeeding period Infants until 2 years of age</p> <p>Arm 1: Controls Description Olive oil Manufacturer Santagata Luigi s.r.l., Genova, Italia N-3 Composition. Dose 3 g/day for mothers, 1 mL/day for infants Blinding NR "double-blind" ALA 0 DHA 0 EPA 0 EPA-DHA 0 AA 0 Total N-3 0 Other dose 1 LA (18:2n-6): 9 weight% of total Arm 2: Intervention Description Blackcurrant seed oil Manufacturer Aromtech Ltd, Tornio, Finland N-3 Compositions shown in Table 1 Dose 3 g/day for mothers, 1 mL/day for infants ALA 14 weight% of total DHA 0 EPA 0 EPA-DHA 0 AA 0 Total N-3 17 weight% of total Other comment 1 SDA: 3 weight% of total</p>	<p>Outcome birth weight Follow-up time birth Arm 1 Sample size 129 mean 3599 SD (468) Arm 2 Sample size 112 mean 3595 SD (461)</p>
<p>Lucia Bergmann et al., 2007⁴⁰</p> <p>Study name: NR</p> <p>Study dates: 2000-2002</p> <p>Study design: Trial randomized parallel</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 144 Pregnant withdrawals 51 Pregnant completers 69</p> <p>Pregnant age: 31 (DHA</p>	<p>Inclusion Criteria: at least 18 years of age and willing to breastfeed for at least three months were enrolled at 21 weeks' gestation during the period October 2000 to August 2002</p>	<p>Start time: Pregnant 21th week</p> <p>Duration: Pregnant 37th week</p> <p>Arm 1: Vitamins and minerals Manufacturer Nestle' (Vevey, Switzerland) Arm 2: Prebiotic Description basic supplement plus the prebiotic, fructooligosaccharide (FOS) (4.5 g)</p>	<p>Outcome birth weight Follow-up time birth Arm 1 Sample size 74 mean 3548 SD (469.3) Arm 3 Sample size 43 mean 3427 SD (493.6)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Location: Germany</p> <p>Funding source / conflict: NR</p>	<p>4.69; control 4.89)</p> <p>Infant age: DHA 39.1; control 39.5 weeks (DHA 1.64; control 1.38)</p> <p>Race of Mother: White European (100)</p>	<p>Exclusion Criteria: increased risk of premature delivery or multiple pregnancy, allergy to cow milk protein, lactose intolerance, diabetes, smoking, consumption of alcohol (>20 g/week), or participation in another study. Infants excluded if they were premature at birth (<37 week gestation, or had any major malformations or hospitalized for more than one week.</p>	<p>Manufacturer Nestle´ (Vevey, Switzerland)</p> <p>Active ingredients fructooligosaccharide (FOS) (4.5 g)</p> <p>Arm 3: DHA</p> <p>Description basic supplement with FOS and DHA (200 mg)</p> <p>Manufacturer Nestle´ (Vevey, Switzerland)</p> <p>Dose 200 mg DHA prepared from fish oil (assuming that some EPA but dose was not reported)</p> <p>DHA 200 mg</p> <p>EPA NR</p>	
<p>Mozurkewich et al., 2013⁴¹</p> <p>Study name: NR</p> <p>Study dates: Oct 2008 - may 2011</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 126 Pregnant withdrawals 8 Pregnant completers 118</p> <p>Pregnant age: EPA 29.9; DHA 30.6; placebo 30.4 (EPA 5.0; DHA 4.5; placebo 5.9)</p> <p>Race of Mother: White European (85%; 76%; 83%) Black (10%; 11%; 5%) Asian (3%; 3%; 2%) Hispanic (0%; 11%; 7%) Inuit Eskimo (0%; 0%; 2%) Pacific Islander (NR)</p>	<p>Inclusion Criteria: past history of depression, an EPDS score 9-19 (at risk for depression or mildly depressed), singleton gestation, a maternal age of 18 years or older, and a gestational age of 12-20 weeks</p> <p>Exclusion Criteria: had a history of a bleeding disorder, thrombophilia requiring anticoagulation, multiple gestation, bipolar disorder, current major depressive disorder, current substance abuse, lifetime substance dependence, or schizophrenia. Women were also ineligible if they were currently taking omega-3 fatty acid supplements or</p>	<p>Start time: Pregnant 12-20 week gestation</p> <p>Duration: Pregnant assuming till birth</p> <p>Arm 1: Control/Placebo</p> <p>Description 98% soy oil and 1% each of lemon and fish oil</p> <p>Manufacturer Nordic Naturals Corporation in Watsonville, CA</p> <p>Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C.</p> <p>Dose 2 large and 4 small placebo capsules</p> <p>Blinding The placebos were formulated to be identical in appearance to both the EPA- and DHA-rich supplements</p> <p>Arm 2: EPA-rich fish oil</p> <p>Description an approximate 4:1 ratio of EPA to DHA (1060 mg EPA plus 274 mg DHA)</p> <p>Brand name ProEPAXtra, Nordic Naturals</p> <p>Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C.</p> <p>Dose 2 large EPA capsule and 4 small placebo DHA 274 mg</p> <p>EPA 1060 mg</p> <p>Arm 3: DHA-rich fish oil</p> <p>Description DHA and EPA in an approximate 4:1</p>	<p>Outcome birth weight</p> <p>Follow-up time birth</p> <p>Arm 1 Sample size 40 mean 3309 SD (555)</p> <p>Arm 2 Sample size 40 mean 3402 SD (550)</p> <p>Arm 3 Sample size 38 mean 3774 SD (438)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		antidepressant medications or eating more than 2 fish meals per week.	ratio o (900 mg DHA plus 180 mg EPA) Brand name ProDHA, Nordic Naturals Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose 2 large placebo oil and 4 small DHA rich DHA 900 mg EPA 180 mg	
Stein et al., 2011 ³³ Study name: NR Study dates: 02. 2005-02.2007 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government	Study Population: Healthy infants Pregnant enrolled 1094 Pregnant completers 973 Pregnant age: placebo 26.3; DHA 26.4 (placebo 4.6; DHA 4.9) Infant age: 39.1 (placebo 1.6; DHA 1.8) Race of Mother: NR	Inclusion Criteria: women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breast-fed for at least 3 mo, and to live in the area for at least 2 y after delivery Exclusion Criteria: NR	Start time: Pregnant 18-22 Gestinal week Infants birth Duration: Pregnant birth Arm 1: Placebo Description Olive oil Manufacturer Martek Biosciences Dose 2 capsules olive oil Blinding Similar in appearance and taste to DHA capsules Arm 2: DHA Description algal DHA capsules Manufacturer Martek Biosciences Dose 2 capsules * 200mg DHA 400 mg	Outcome birth weight Follow-up time birth Arm 1 Sample size 370 mean 3220 SD (475) Arm 2 Sample size 369 mean 3242 SD (441)
Tofail et al., 2006 ⁸¹ Study name: NR Study dates: enrollment January to March 2000 Study design: Trial randomized parallel Location: Bangladesh Funding source / conflict: Government Follow-up: 10 months	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 400 Pregnant completers 151 Pregnant age: 22.7 years (4.35 years) NR Race of Mother: Asian (100%)	Inclusion Criteria: seems as if all pregnant women at 25 weeks gestation were enrolled, no inclusion criteria specified Exclusion Criteria: NR	Start time: Pregnant 25 weeks gestation Duration: Pregnant until birth Arm 1: placebo Description soy oil capsule N-3 Composition. Dose 4 one gram capsules per day Blinding capsules were identical in appearance Other dose 1 LNA 0.27 g Other dose 2 linoleic acid 2.25 g Arm 2: DHA supplement Description fish oil capsules Dose 4 one gram capsules per day DHA 1.2 g EPA 1.8 g	Outcome birth weight Follow-up time birth Arm 1 Sample size 124 mean 2.7 SD (0.4) Arm 2 Sample size 125 mean 2.7 SD (0.4)
Ramakrishnan et al., 2010 ³¹	Study Population: Healthy pregnant women	Inclusion Criteria: 18-35 yrs. of age, in gestation	Start time: Pregnant at study entry	Outcome birth weight Follow-up time birth

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study name: POSGRAD</p> <p>Study dates: feb 2005 - feb 2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: Mexico</p> <p>Funding source / conflict: Government, March of Dimes</p> <p>Follow-up: 840</p> <p>Follow-up article(s) ^{32, 72}</p>	<p>Pregnant enrolled 1,094 Pregnant withdrawals 67 Pregnant completers 973 (for birthweight)</p> <p>Pregnant age: 26.2 (controls) 26.3 (DHA) (4.6 (controls) 4.8 (DHA))</p> <p>Race of Mother: Hispanic (NR)</p>	<p>weeks 18-22, planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breastfeed for at least 3 months, liver in the area for at least 2 years after delivery.</p> <p>Exclusion Criteria: high-risk pregnancy; lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplements; chronic use of certain medications (e.g., medications for epilepsy).</p>	<p>Duration: Pregnant mid pregnancy (18-22 weeks gestation) until delivery</p> <p>Arm 1: Controls Description Placebo containing olive oil Manufacturer Martek Biosciences Dose 1 capsule, twice a day Blinding Identical tablets</p> <p>Arm 2: DHA Description Intervention Manufacturer Martek Biosciences N-3 Composition 200 mg DHA derived from algal source Dose 1 capsule twice a day DHA 400 mg/d</p>	<p>Arm 1 Sample size 486 mean 3202 SD (472) Arm 2 Sample size 487 mean 3207.2 SD (449.4)</p>

Table 8. Observational studies for Birth Weight

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Badart-Smook, et al., 1997⁴⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: NR</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 610 Pregnant withdrawals 240 Pregnant completers 370</p> <p>Pregnant age: 29 (4)</p> <p>Race of Mother: White European (100)</p>	<p>Inclusion Criteria: White race, intention to give birth to the baby in one of the three hospitals involved in the study</p> <p>Exclusion Criteria: Women with diastolic blood pressure of 90mm or higher, women suffering from any metabolic, cardiovascular, neurological, or renal disorder</p>
<p>Much, et al., 2013⁷¹</p> <p>Study name: INFAT</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Germany</p> <p>Funding source / conflict: Industry, Government, Some authors employed by industry (companies that make the supplements), Multiple foundations and Societies, None</p> <p>Follow-up article(s) ⁶⁹, ⁷⁰, ³⁶</p>	<p>Study Population: Healthy infants Breast-feeding women</p> <p>Pregnant enrolled 208</p> <p>Infants completers 187</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: Healthy pregnant women at 14th week of gestation</p> <p>Exclusion Criteria: None reported</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Drouillet, et al., 2009⁸³</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: NR</p> <p>Funding source / conflict: Industry, Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 2002 Pregnant completers 1446</p> <p>Pregnant age: 29.2 (4.8)</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: twin pregnancies, known diabetes before pregnancy, not being able to speak and read French, and planned moving away from the region</p>
<p>Brantsaeter, et al., 2012⁸⁴</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Norway</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 76218 Pregnant completers 62099</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: first participation for women with multiple participation in MoBa and women with singleton births.</p> <p>Exclusion Criteria: participants with a pregnancy duration <28 weeks or >42 weeks (n=628), if the birth weight of the baby had not been recorded or if the birth weight was, <600 g (n = 35). We also excluded participants who had not given birth to a live baby (n 153). Lastly, we excluded women having improbable energy intakes, i.e. energy intake , >4.5 MJ or .<20 MJ (n 1063)</p>
<p>Smits, et al., 2013⁷⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: None</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 1659 Pregnant completers 1659</p> <p>Infants enrolled 1659 Infants completers 1659</p> <p>Pregnant age: <25 y, 5.7% 25-34 y, 61.2% >=35 y, 33.1%</p> <p>Infant age: 40.0 weeks (1.2)</p> <p>Race of Mother: White European (88.4)</p>	<p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: primiparous women or delivered preterm</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Dirix, et al., 2009⁸⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 1238 Pregnant completers 782</p> <p>Infants enrolled 1238 Infants completers 782</p> <p>Pregnant age: 29.0 26.2-31.7</p> <p>Infant age: 40.1 wk 39.3-41.0</p> <p>Race of Mother: White European (100)</p>	<p>Inclusion Criteria: gestational age of <16 weeks at study entry, singleton pregnancy, Caucasian race, diastolic blood pressure, 90 mmHg and the absence of any metabolic, cardiovascular, neurological or renal disorder at the time of recruitment</p> <p>Exclusion Criteria: excluded if infants were born preterm (gestational age < 37 weeks,), mothers had diabetes or developed pregnancy-induced hypertension, mothers had reported specific health problems in the past (e.g. diabetes mellitus, hypertension and heart, kidney, liver, gall bladder or thyroid gland disorders, one or both parents were non-Caucasians or values for any of the aforementioned exclusion criteria were missing. The mother – infant pairs were also excluded if fatty acid analyses were not reported or values were missing for birth weight, birth length and head circumference</p>
<p>Oken, et al., 2004⁴⁵</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: US</p> <p>Funding source / conflict: Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 2109 Pregnant completers 2109</p> <p>Pregnant age: 14-<20, 3% 20-<25, 6% 25-<30, 21% 30-<35, 42% 35=<40, 23% >=40, 4% (14-44)</p> <p>Race of Mother: White European (66) Black (16) Asian (6) Hispanic (7) Other race/ethnicity (4)</p>	<p>Inclusion Criteria: delivered a live infant, and completed at least one dietary questionnaire</p> <p>Exclusion Criteria: taking cod liver or fish oil supplement</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Olafsdottir, et al., 2005⁸⁵</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: NR</p> <p>Funding source / conflict: Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 436 Pregnant completers 436</p> <p>Pregnant age: No 27.8; Yes 29.6 (no 4.9; yes 4.6)</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: absence of pre-eclampsia, hypertension or diabetes mellitus</p> <p>Exclusion Criteria: women whose personal data could not be found or who moved abroad before giving birth (n 8), had a miscarriage or stillbirth (n 17), twins or triplets (n 5), a preterm birth hypertension/pre-eclampsia (n 62) or gestational diabetes mellitus (n=4)</p>

Antenatal and postnatal depression

Key Findings and Strength of Evidence for Antenatal and/or postnatal depression outcome

- Three RCTs assessing the effects of prenatal supplementation with DHA alone, DHA+AA, or EPA-enriched fish oil found no effects on either antenatal or postnatal depression among healthy pregnant women.
- Two prospective observational studies found no associations between prenatal dietary or supplemental n-3 FA intake and antenatal or postnatal depression.
- One prospective observational study found a weak association between prenatal EPA levels in plasma levels and perinatal onset depression. No association was found between n-3FA levels and antenatal or postnatal depression.
- One RCT assessing the effects of postnatal supplementation with DHA alone found no effects on postnatal depression.

This outcome is an additional outcome of interest that was not included in the original review. A total of four eligible RCTs and four observational studies were identified. Of these eight studies, three RCTs and all of the observational studies evaluated the effects of prenatal maternal n-3 FA interventions or exposures, while the fourth RCT examined the effects of postnatal maternal n-3 FA interventions or exposures. All studies that assessed the effects of n-3 FA on antenatal or postnatal depression were conducted among healthy, pregnant or lactating women.

Prenatal maternal n-3FA interventions/exposures

Randomized Controlled Trials

Three RCTs assessed the effects of prenatal maternal supplementation on the risk for antenatal and/or postnatal depression.^{34, 41, 89} While all of the studies compared the effects of DHA (200 to 900 mg/day) to that of placebo, two studies also included a third study arm. One included a third arm with supplements containing DHA+AA⁸⁹, and the other included a third arm with supplements containing EPA-rich fish oil.⁴¹ One study examined the effects of n-3 FAs on postnatal depression only³⁴, while the other two RCTs examined the effects on both antenatal and postnatal depression.^{41, 89} None of the studies found any significant effects of marine oils on ante- or postnatal depression outcomes compared with placebo.

The DOMInO trial randomized 2,399 pregnant Australian women (<21 week's gestation) to receive fish oil containing 0.80 g/day DHA and 0.10 g/day EPA (n=1197) or vegetable oil placebo (n=1202) and followed women up to six months postpartum to assess for depressive symptoms using the Edinburgh Postnatal Depression Scale (EPDS).³⁴ The duration of intervention was not reported. No differences were found in percentage of women reporting high levels of depressive symptoms (EPDS score >12) at either 6 weeks or 6 months postpartum between groups.

Doornbos et al (2009) enrolled 182 pregnant Dutch women (14-20 weeks gestation) into a three-arm trial (0.220 g/day DHA+ 0.220 g/day AA vs. 0.220 g/day DHA vs. soybean oil placebo)⁸⁹. Sixty three women dropped out prior to 36 weeks gestation, leaving data from 119

women available for analysis. No differences were found in median EPDS scores among the groups at either week 36 of pregnancy or 6 months postpartum.

Mozurkewich et al (2013) enrolled 126 pregnant women in the U.S. (12-20 weeks gestation) into a three arm trial (0.900 g/d DHA+0.180 g/d EPA vs. 1.060 g/d EPA+274 g/d DHA vs. soy oil placebo). After adjusting for baseline BDI scores, no differences were found in mean Beck Depression Inventory (BDI) score between groups at either 34-36 weeks' gestation or 6-8 weeks postpartum. However, a trend was observed toward significance at 26-28 weeks' gestation ($p=0.05$).

Observational studies

Four prospective studies were identified that assessed the effects of prenatal maternal n-3 FA intake or status on antenatal, perinatal, or postnatal depression. Two studies measured dietary n-3 FA intake,^{90, 91} one study measured n-3 supplement intake,⁹² and one study measured the percent of total red blood cell phospholipid FAs.⁹³

Dietary n-3 FA intake

Strom et al (2009) analyzed data from 54,202 women enrolled in the Danish National Birth Cohort.⁹⁰ They examined the association between deciles of n-3 FA intake estimated from a food frequency questionnaire administered mid-pregnancy and either admittance to a psychiatric hospital due to postpartum depression (PPD-admission) or purchase of antidepressants in a pharmacy with a prescription (PPD-prescription). No association was seen between any decile of intake of n-3 FAs and risk of either PPD-admission or PPD-prescription after adjusting for confounders.

Miyake et al (2006) assessed the association of n-3 FA intake with risk of postpartum depression among 865 Japanese women enrolled in the Osaka Maternal and Child Health Study (OMCHS).⁹¹ The authors observed no significant dose-response relationship between intakes of total n-3 FAs, EPA, DHA, or n-3/n-6 FA ratio and postpartum depression (as measured by the EPDS), even after adjusting for confounders.

Supplementary n-3 FA intake

Leung et al (2013) analyzed data from 475 Canadian women enrolled in the Alberta Pregnancy Outcomes and Nutrition (APrON) study who completed the EPDS questionnaire at least twice during pregnancy and at 12 weeks postpartum.⁹² Mean supplementary intake of n-3 FA differed significantly between women with a postpartum EPDS score <10 ($n=416$) and those with a postpartum EPDS score ≥ 10 ($n=59$) (180 vs. 90 mg, $p=0.01$); however, the association did not persist in multivariate analyses. No association was observed between supplementary n-3 FA intake and prenatal EPDS scores measured in the second and third trimesters.

Percent total RBC phospholipid FAs

Sallis et al (2014) reported results from 3,397 women enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort in England.⁹³ The authors examined the association between percent of total RBC phospholipid FAs measured from antenatal blood samples and ante-, peri-, and post-natal depression as measured by the EPDS. EPDS score >12 was the cutoff used to define depression. A weak association between prenatal EPA levels and perinatal onset depression was observed after adjusting for social class and maternal age (OR 1.07, 95% CI 0.99, 1.15). Levels of n-3 FAs were not associated with antenatal or postnatal depression in multivariate models.

Postnatal maternal n-3 FA interventions/exposures

Randomized Controlled Trials

One RCT conducted in the U.S. that assessed the effects of a postnatal intervention on risk for PPD was identified.⁹⁴ Llorente et al (2003) enrolled 138 pregnant women who planned to breast feed for at least 4 months to receive an algae-derived triglyceride capsule containing 0.200 g/day of DHA or placebo, beginning within a week of delivery for four months. Eighty nine (64%) lactating women, mean age 31.5 years, completed four months of the study (44 in the DHA group and 45 in the placebo group) and were assessed for depressive symptoms using the BDI. Sixty three (46%) women were followed up to 18 months (31 in the DHA group and 32 in the placebo group) and were assessed for depressive symptoms using the EPDS. No significant differences in depressive symptom scores were found between groups at any of the time points (3 weeks, 2 months, 4 months, or 18 months postpartum).

Table 9. RCTs for Ante postnatal depression

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Makrides et al., 2010³⁴</p> <p>Study name: DOMInO</p> <p>Study dates: 2005-2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up article(s) ^{48, 49, 50, 51, 52, 53, 3}</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 2399 Pregnant withdrawals 1</p> <p>Infants enrolled 605 Infants withdrawals 32 Infants completers 726</p> <p>Pregnant age: 28.9 (DHA5.7; control5.6)</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: with singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments</p> <p>Exclusion Criteria: already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home</p>	<p>Start time: Pregnant < 21 week's gestation</p> <p>Duration: NR</p> <p>Arm 1: vegetable oil capsules Description a blend of 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Manufacturer Efamol, Surrey, England. Dose 3* 500mg capsule / day</p> <p>Blinding All capsules were similar in size, shape, and color</p> <p>Arm 2: DHA Description DHA-rich fish oil concentrate Manufacturer ; Incromega 500 TG, Croda Chemicals, East Yorkshire, England Dose 500mg capsule *3/day DHA 800mg EPA 100mg</p>	<p>Outcome % with Edinburgh Postnatal Depression Scale (EPDS) > 12</p> <p>Follow-up time 6 months</p> <p>Arm 1 138/1202 (11.5%) Arm 2 117/1197 (9.74%)</p> <p>Follow-up time 6 weeks</p> <p>Arm 1 131/1202 (10.88%) Arm 2 115/1197 (9.61%)</p>
<p>Doornbos et al., 2009⁸⁹</p> <p>Study name: NR</p> <p>Study dates: Not reported</p> <p>Study design: Trial randomized parallel</p> <p>Location: Netherlands</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 182 Pregnant withdrawals 63 Pregnant completers 119</p> <p>Pregnant age: NR (NR) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: women with first or second, singleton pregnancies</p> <p>Exclusion Criteria: women with a vegetarian or vegan diet or gestational diabetes and preterm delivery (<37 weeks)</p>	<p>Start time: Pregnant 16.5 (14-20) week of pregnancy</p> <p>Duration: Pregnant till 3 months after delivery</p> <p>Arm 1: Control group Description Placebo-soybean oil</p> <p>Arm 2: DHA group Brand name NR Manufacturer NR DHA 220mg</p> <p>Arm 3: DHA + AA group Brand name NR</p>	<p>Outcome Edinburgh Postnatal Depression Scale (EPDS)</p> <p>Follow-up time 36 weeks pregnant</p> <p>Arm 1 Sample size 34 median 4 IQR (2.5, 9.0) Arm 2 Sample size 40 median 4 IQR (2.0, 7.0) Arm 3 Sample size 37 median 6 IQR (3.0, 10.0)</p> <p>Follow-up time 6 weeks post-partum</p> <p>Arm 1 Sample size 32 median 5 IQR (2.0, 6.5)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Industry Follow-up: 3 months/12 weeks postpartum 6981			Manufacturer NR DHA 220 mg AA 220mg	Arm 2 Sample size 38 median 4 IQR (2.5, 7.0) Arm 3 Sample size 30 median 5 IQR (2.0, 6.0)
Mozurkewich et al., 2013 ⁴¹ Study name: NR Study dates: Oct 2008 - may 2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 126 Pregnant withdrawals 8 Pregnant completers 118 Pregnant age: EPA 29.9; DHA 30.6; placebo 30.4 (EPA 5.0; DHA 4.5; placebo 5.9) Race of Mother: White European (85%; 76%; 83%) Black (10%; 11%; 5%) Asian (3%; 3%; 2%) Hispanic (0%; 11%; 7%) Inuit Eskimo (0%; 0%; 2%) Pacific Islander (NR)	Inclusion Criteria: past history of depression, an EPDS score 9-19 (at risk for depression or mildly depressed), singleton gestation, a maternal age of 18 years or older, and a gestational age of 12-20 weeks Exclusion Criteria: had a history of a bleeding disorder, thrombophilia requiring anticoagulation, multiple gestation, bipolar disorder, current major depressive disorder, current substance abuse, lifetime substance dependence, or schizophrenia. Women were also ineligible if they were currently taking omega-3 fatty acid supplements or antidepressant medications or eating more than 2 fish meals per week.	Start time: Pregnant 12-20 week gestation Duration: Pregnant assuming till birth Arm 1: Control/Placebo Description 98% soy oil and 1% each of lemon and fish oil Manufacturer Nordic Naturals Corporation in Watsonville, CA Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose 2 large and 4 small placebo capsules Blinding The placebos were formulated to be identical in appearance to both the EPA- and DHA-rich supplements Arm 2: EPA-rich fish oil Description an approximate 4:1 ratio of EPA to DHA (1060 mg EPA plus 274 mg DHA) Brand name ProEPAXtra, Nordic Naturals Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose 2 large EPA capsule and 4 small placebo DHA 274 mg EPA 1060 mg Arm 3: DHA-rich fish oil Description DHA and EPA in an approximate 4:1 ratio of (900 mg DHA plus 180 mg EPA) Brand name ProDHA, Nordic Naturals Viability centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose 2 large placebo oil and 4 small DHA rich DHA 900 mg EPA 180 mg	Outcome Beck Depression Inventory (BDI) Follow-up time 26-28 weeks Arm 1 Sample size 41 mean 6.3 SD (3.9) Arm 2 Sample size 39 mean 8.7 SD (4.2) Arm 3 Sample size 38 mean 7 SD (4.6) Follow-up time 34-36 weeks Arm 1 Sample size 41 mean 7.4 SD (5.5) Arm 2 Sample size 39 mean 8.2 SD (5.7) Arm 3 Sample size 38 mean 6.9 SD (6.3) Follow-up time 6-8 weeks post-partum Arm 1 Sample size 41 mean 5.9 SD (6.1) Arm 2 Sample size 39 mean 6.6 SD (5.2) Arm 3 Sample size 38 mean 5.7 SD (4.8)
Llorente et al., 2003 ⁹⁴ Study name: Unnamed Trial A	Study Population: Breast-feeding women Lactating enrolled 138	Inclusion Criteria: pregnant women who were 18 to 42 years old and planned to breast	Start time: Lactating birth Duration: Lactating 4 months	Outcome Beck Depression Inventory (BDI) Follow-up time 2 months Arm 1 Sample size 45 mean 4.4 SD (4.2) Arm 2 Sample size 44 mean 5.5 SD (4.3)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study dates: <2002</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up: 18 months</p> <p>Follow-up article(s) ^{95, 96, 97}</p>	<p>Lactating completers 101</p> <p>Lactating enrolled 138</p> <p>Lactating completers 101</p> <p>Lactating age: 31.5 years (4.5 years) 18 - 42</p> <p>Race of Mother: White European (82%) Black (14%) Hispanic (2.3%) Other race/ethnicity (1.6%)</p>	<p>feed for at least 4 months</p> <p>Exclusion Criteria: those with chronic medical conditions, or taking dietary supplements other than vitamins, or smokers, or who had been pregnant >5 times</p>	<p>Arm 1: placebo</p> <p>Description placebo capsule</p> <p>Manufacturer Martek Biosciences Corporation, Columbia, Md</p> <p>Dose 1 capsule</p> <p>Blinding capsules were identical in appearance</p> <p>Arm 2: omega 3 capsule</p> <p>Description algae-derived triglyceride capsule</p> <p>Brand name DHASCO</p> <p>Manufacturer Martek Biosciences Corporation, Columbia, Md</p> <p>Dose 1 capsule</p> <p>DHA 200 mg</p>	<p>Follow-up time 3 weeks</p> <p>Arm 1 Sample size 45 mean 6.3 SD (4.7)</p> <p>Arm 2 Sample size 44 mean 7.1 SD (5.7)</p> <p>Follow-up time 4 months</p> <p>Arm 1 Sample size 45 mean 4.8 SD (5.9)</p> <p>Arm 2 Sample size 44 mean 5.8 SD (5.2)</p> <p>Outcome Edinburgh Postnatal Depression Scale (EPDS)</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 32 mean 6.3 SD (4.1)</p> <p>Arm 2 Sample size 31 mean 6.3 SD (5.2)</p> <p>Outcome responder: BDI<10</p> <p>Follow-up time at either 2, 4 or 18 months</p> <p>Arm 1 36/45 (79%)</p> <p>Arm 2 33/44 (76%)</p> <p>Outcome responder: BDI<20</p> <p>Follow-up time at either 2, 4 or 18 months</p> <p>Arm 1 43/45 (95.5%)</p> <p>Arm 2 40/44 (91.1%)</p>

Table 10. Observational studies for Ante postnatal depression

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Strom, et al., 2009⁹⁰</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Denmark</p> <p>Funding source / conflict: Government, Multiple foundations and Societies, Funding Affiliations trade group, March of Dimes</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 86,453 Pregnant withdrawals 32,251 Pregnant completers 54,202</p> <p>Pregnant age: not reported (not reported) not reported</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: All pregnant women living in Denmark between 1996 and 2002, who were fluent in Danish</p> <p>Exclusion Criteria: NR</p>
<p>Sallis, et al., 2014⁹³</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: NR</p> <p>Funding source / conflict: Industry, Government</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 14,541 Pregnant withdrawals 11,144 Pregnant completers 3,397</p> <p>Pregnant age: 28.9 (4.5) not reported</p> <p>Race of Mother: White European (100%)</p>	<p>Inclusion Criteria: All women with an expected due date between April 1991 and December 1992 were eligible for the study. Only women with data available on genotype, FA levels and depressive symptoms during pregnancy or at 8 weeks postnatally and women with a self-reported ethnicity of White European were included in this analysis.</p> <p>Exclusion Criteria: Mothers who lost a child during the neonatal period and those with a still birth; mothers with multiple births.</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Leung, et al., 2013⁹²</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Canada</p> <p>Funding source / conflict: NR</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 600 Pregnant withdrawals 125 Pregnant completers 475</p> <p>Pregnant age: 31.2 not depressed 31.6 depressed (4.16 not depressed 4.7 depressed) not reported</p> <p>Race of Mother: White European (87%) Other race/ethnicity (13%)</p>	<p>Inclusion Criteria: at least 16 years old with gestational age <=27 weeks. Women must be in the first (T1) or second (T2) trimester</p> <p>Exclusion Criteria: Any woman who was 28 weeks or beyond, Non-English speakers, known drug and alcohol abusers, and those planning to move out of the region within 6 months</p>
<p>Yoshihiro Miyake, et al., 2006⁹¹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Japan</p> <p>Funding source / conflict: Government, Multiple foundations and Societies, None</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 1002 Pregnant withdrawals 137 Pregnant completers 865</p> <p>Pregnant age: age reported in categories</p> <p>Race of Mother: Asian (100%)</p>	<p>Inclusion Criteria: women who became pregnant in Neyagawa City, Osaka Prefecture, Japan</p> <p>Exclusion Criteria: NR</p>

Key Question 2: Fetal/childhood exposures

What is the influence of maternal intakes of n-3 fatty acids or the n-3 fatty acid content of maternal breast milk (with or without knowledge of maternal intake of n-3 FA) or n-3 FA-supplemented infant formula or intakes of n-3 FA from sources other than maternal breast milk or supplemented infant formula on the following outcomes in term or preterm human infants?

- Postnatal Growth patterns
- Neurological development
- Visual function
- Cognitive development
- **Autism**
- **Learning disorders**
- **ADHD**
- **Atopic dermatitis**
- **Allergies**
- **Respiratory illness**

What are the associations of the n-3 FA content or the n-6/n-3 FA ratio of maternal or fetal or child biomarkers with each of the outcomes identified above?

Postnatal Growth Patterns

Key Findings and Strength of Evidence

- There is moderate evidence that prenatal maternal supplementation of fish oil or DHA+EPA supplements has no effect on weight, length, or head circumference at 18 months. Pooled analysis of 5 RCTs shows null effects for weight (0.22, 95% CI [-0.62, 0.19]), length (0.01 [-0.52, 0.54]), and head circumference (-0.01 [-0.28, 0.27]).
- There is low evidence that prenatal maternal supplementation of fish oil or DHA+EPA supplements continuing postpartum has no effect on growth outcomes.
- There is low evidence that supplementation of DHA+AA formula in preterm infants has no effect on overall weight and length. Pooled analysis of three studies showed null effects for weight at 4 months (-0.01 [-0.48, 0.47]) and length at 4 months (-0.03 [-0.91, 0.85]).
- There is low evidence that supplementation of DHA+AA formula in term infants has no effect on growth outcomes.
- There is low evidence from three observational studies that biomarkers associated with n-3s in infant red blood cells are consistently associated with increased weight gain, length gain, and BMI at 7 years.
- There is insufficient evidence to determine whether prenatal and postnatal maternal supplementation with DHA+AA has an effect on growth outcomes.
- There is insufficient evidence to determine whether postnatal maternal supplementation with DHA+EPA has an effect on growth outcomes.
- There is insufficient evidence to determine whether prenatal maternal supplementation in combination with postnatal infant supplementation with DHA+EPA has an effect on growth outcomes.

- There is insufficient evidence to determine whether supplementation of preterm infants with DHA+AA+EPA has an effect on growth outcomes.

Description of Included Studies

The original review included 42 RCTs and two observational studies for the outcomes of postnatal growth patterns, including one RCT assessing the effects of prenatal maternal intake of n-3 FAs during pregnancy in term and preterm infants; one RCT and one cohort study on n-3 FA content of breast milk with or without known maternal intake in term infants only (no studies assessed the effects of n-3 FA intake by breastfeeding mothers on growth patterns of preterm infants); 20 RCTs on postnatal n-3 FA supplementation in preterm infants; 18 RCTs on postnatal n-3 FA supplementation in term infants; five RCTs that also assessed associations of n-3 FA biomarkers with growth patterns of preterm infants; five RCTs and a prospective cohort study that assessed associations of n-3 FA biomarkers with postnatal growth patterns in term infants; and one RCT that assessed the associations of n-3 FA biomarkers with postnatal growth patterns in very low birth weight (VLBW) term and preterm infants.

The present review identified 20 additional RCTs and three observational studies that included pediatric growth pattern outcomes. Three of the RCTs also included associations of growth patterns with biomarkers of n-3 FA. Of these, five RCTs and two observational studies evaluated prenatal maternal n-3 FA interventions or exposures, one RCT and one observational study examined postnatal maternal n-3 FA interventions or exposures, and three RCTs examined a combination of prenatal and postnatal maternal n-3 FA interventions or exposures. Nine RCTs examined postnatal infant n-3 FA interventions or exposures, and two RCTs examined a mixed set of postnatal maternal and postnatal infant n-3 FA interventions or exposures. Five RCTs that assessed the effects of n-3 FA supplementation in infants on growth patterns were conducted among healthy infants or infants born to healthy women, while six RCTs were conducted among preterm or low birth weight infants.

Prenatal maternal interventions/exposures

In the original review, one good quality RCT found no difference in weight, length, and head circumference from birth to 12 months between infants (590 enrolled, 341 completers) born to mothers who used n-3 FA and n-6 FA supplements or predominantly n-6 FA supplements during pregnancy.

Randomized Controlled Trials

DHA+EPA

The present review identified five studies of prenatal maternal DHA+EPA or fish oil supplementation^{42, 40, 33, 98, 81} and three studies of prenatal and postnatal maternal DHA or fish oil supplementation.^{36, 64, 80}

Dunstan (2008) assessed the effects of prenatal supplementation of 4 g fish oil capsules daily compared to olive oil in 72 pregnant Australian women with allergies starting at 20 weeks of gestation until delivery, but found no differences in infant weight, length, or head circumference at 30 months.⁴²

Bergmann and coworkers (2007) compared the effects of a vitamin and mineral supplement, the supplement plus a prebiotic, and the supplement plus prebiotic and DHA (0.200 g/d) on the offspring of 144 healthy pregnant women in Germany, supplemented from the 21st to 37th

weeks of pregnancy. The authors report that mothers whose supplements included DHA had infants that were not significantly different from the control infants at 1 or 3 months for BMI, weight, length, or head circumference, but BMI (-0.76, 95% CI -1.46, -0.07) and weight (kg) (-0.601, 95% CI -1.46, -0.07) for infants taking DHA were actually less than in control infants at 21 months, although length and head circumference were not significantly different.⁴⁰

Stein and coworkers (2011) randomized 1,094 pregnant Mexican women in weeks 18-22 of gestation to daily olive oil capsules or 0.200 g/d DHA through term.³³ Data from the 739 infants followed up at 18 months indicated no overall effects on weight, length, BMI, or head circumference, although infants born to primigravid women (women pregnant for the first time) supplemented with DHA were significantly longer by 0.7 cm (95% CI 0.1, 1.3; $P = 0.02$).

Similarly, Malcolm and coworkers (2003) randomized 100 pregnant women from 15 weeks gestation until birth to receive either sunflower oil or fish oil (DHA 0.200 g/d) and found no differences in weight, length, or head circumference between the groups at 50 or 66 weeks.⁹⁸

Tofail et al. (2006) compared supplementation of 249 pregnant women in Bangladesh with DHA (1.2 g) and EPA (1.8 g) daily from 25 weeks until delivery with that of soy oil alone, and found no differences in head circumference at 10 months.⁸¹

Van Goor and colleagues (2011) randomized pregnant Dutch women in the 14th-20th weeks of pregnancy to soybean oil capsules with ($n=41$) or without ($n=34$) DHA (0.220 g/d) until 3 months after delivery; again, no significant differences with regard to weight, length, or head circumference were found at 18 months.⁶⁴

We identified a long-term (7-year) follow-up of a study conducted in Norway that was discussed in the original report. In this study, pregnant women were randomized at 18 weeks gestation to receive 10 mL cod liver oil daily (1.183 g/10 mL DHA, 0.803 g/10 mL EPA, and a total of 2.494 g/10 mL *n*-3 PUFAs) or 10 mL corn oil (4.747 g/10 mL LA and 0.092 g/10 mL ALA) through 3 months postpartum. This study found no significant differences in weight, height, or BMI at 7 years.⁸⁰

A study by Hauner et al. (2012) compared the effect of fish oil supplements (DHA 1.020 g/d and EPA 0.180 g/d) and nutritional counseling to that of nutritional counseling alone in German women from 15 weeks gestation to four months postpartum.³⁶ No differences were seen between treatments in weight, length, BMI, or head circumference at 6 weeks, 4 months, or 12 months.

Pooling the results of four RCTs,^{33, 40, 64, 98} on the effects of DHA given to pregnant women compared to placebo on weight, length, and head circumference at 18 months showed no statistically significant effects (WMD [95% CI] in weight (kg): -0.22, [-0.62, 0.19], $I^2=52\%$; WMD [95% CI] in length (cm): 0.01 [-0.52, 0.54], $I^2=0\%$; WMD [95% CI] in head circumference (cm): -0.01, [-0.28, 0.27], $I^2=0\%$). These studies are further summarized in Table 11 and the forest plots are shown in Figures 15, 16, and 17.

Figure 15. Weight (kg) at 18 months – DHA vs. placebo, given to pregnant women

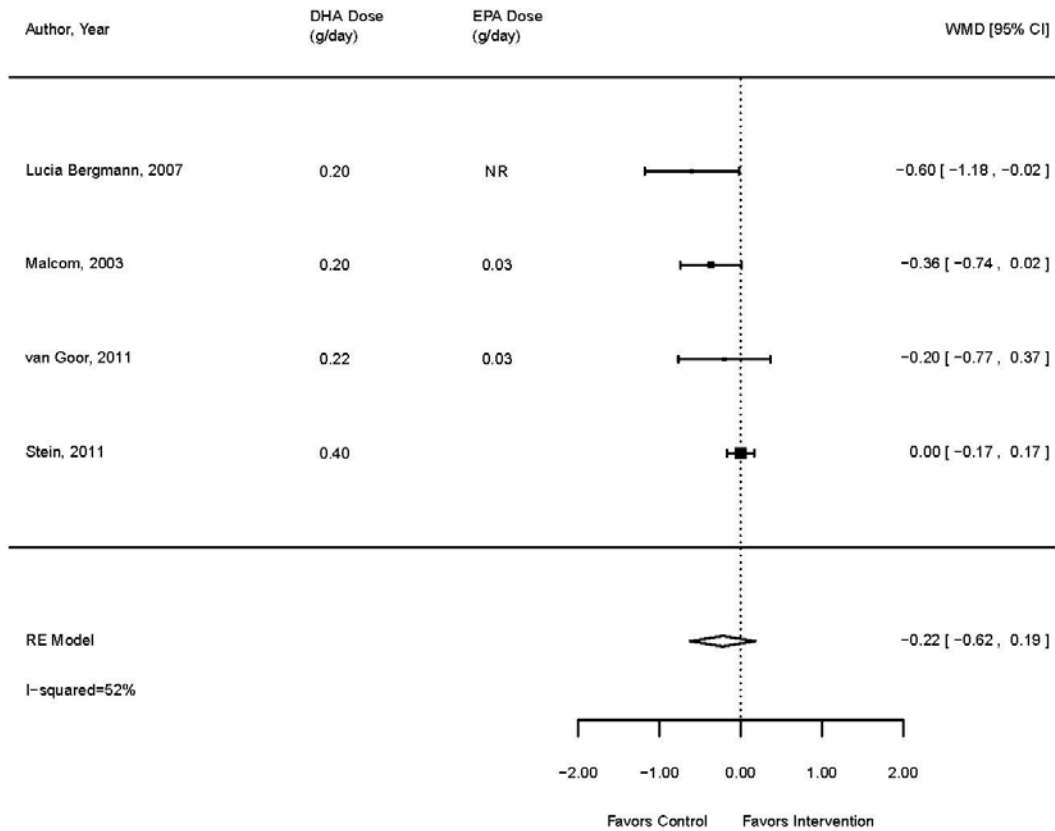


Figure 16. Length (cm) at 18 months – DHA vs. placebo, given to pregnant women

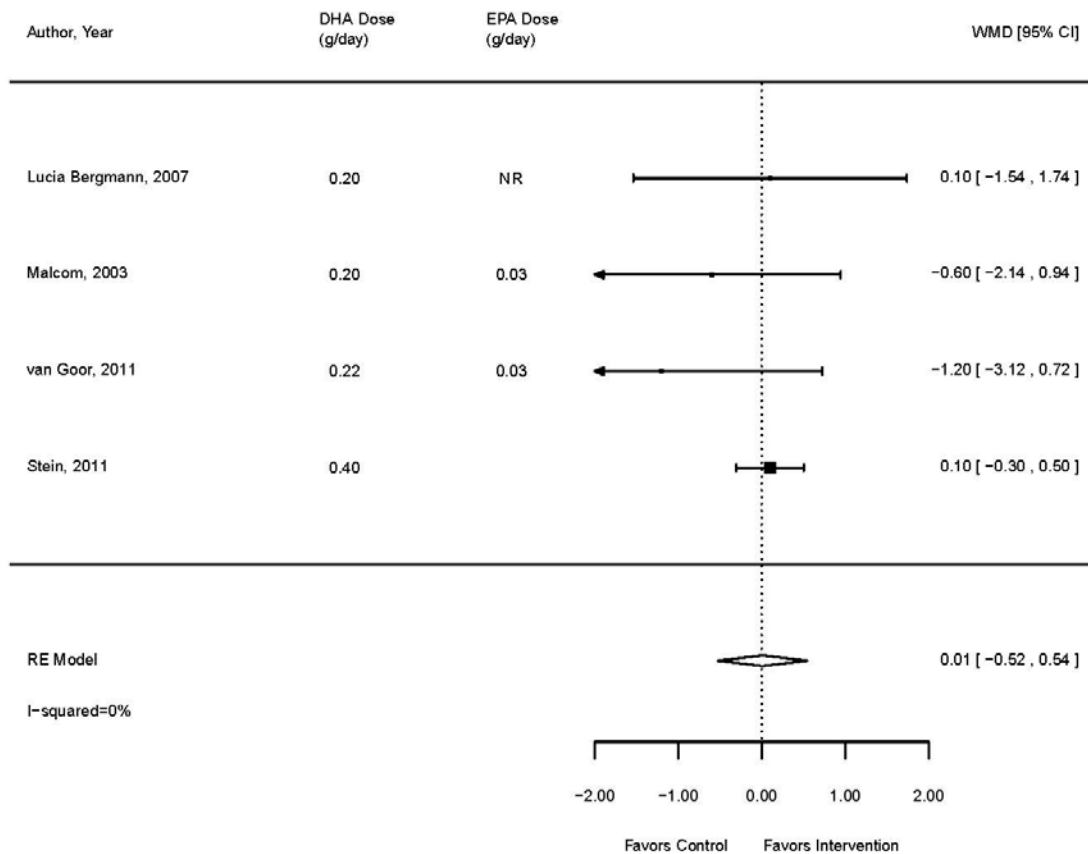
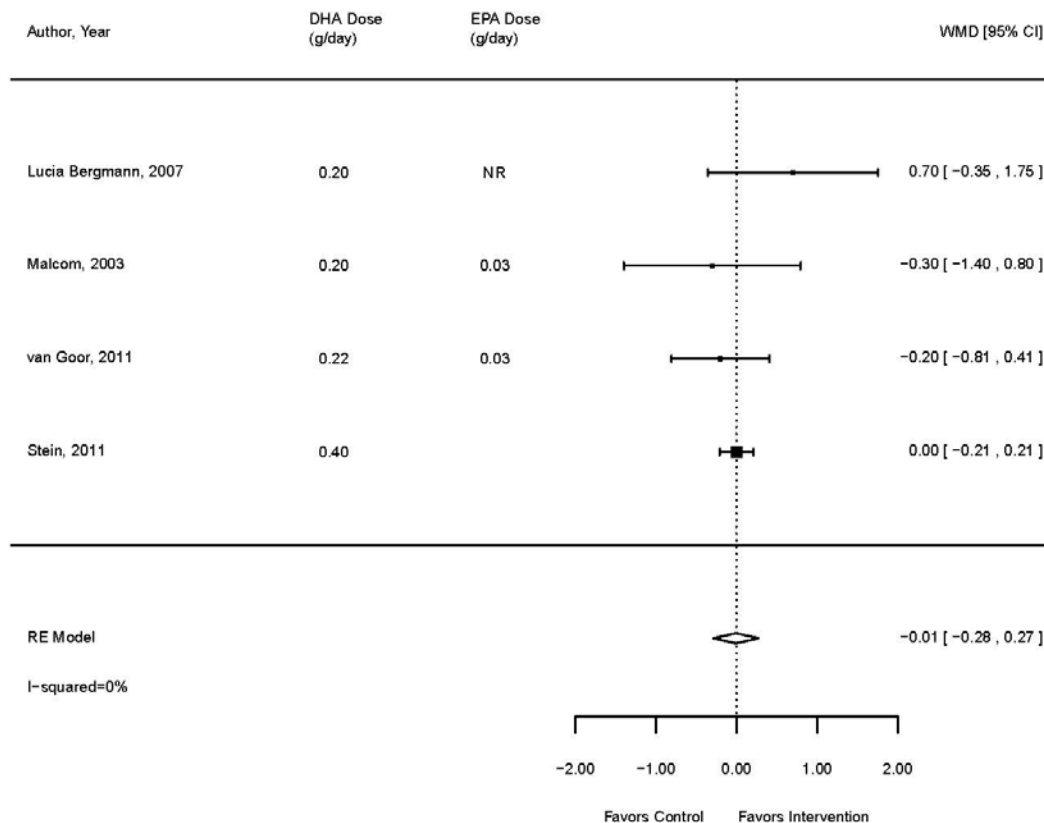


Figure 17. Head circumference (cm) at 18 months – DHA vs. placebo, given to pregnant women



DHA+AA

Only one study was identified that compared the effects on postnatal growth patterns of administering supplemental DHA+AA to pregnant women to that of placebo. Van Goor (2011) randomized pregnant Dutch women in the 14th-20th weeks of pregnancy to soybean oil capsules with (n=39) or without DHA+AA (0.220 g/d) (n=34) until 3 months after delivery. Again, no significant differences with regard to weight, length, or head circumference were found at 18 months.⁶⁴

Observational studies

The outcomes of the INFAT study⁷⁰ were used to assess the association of n-3 FAs in breast milk (in 208 women who had been following their usual diet or supplementing their usual diet with 1.200 g/d LCPUFAs) Negative associations were observed between length at one year and both DHA and n-3 LCPUFA in breast milk (p<0.05); no other significant associations were

observed between breast milk FA concentrations and weight, length, BMI, or head circumference outcomes.

Another analysis of data from the INFAT study⁷¹ found no significant growth outcome associations of LCPUFA content of maternal red blood cells at 32 weeks gestation with weight, length, BMI, or head circumference at 6 weeks, 4 months, or one year (see Table 12).

Postnatal maternal interventions/exposures

The original review identified one good quality RCT, one poor quality RCT, and an observational study on the effect of maternal supplementation of n-3 FA after delivery on postnatal growth patterns. Neither RCT showed effects of maternal intake of n-3 FA or n-6 FA on growth patterns at any time point. The observational study showed a positive correlation between the breast milk AA/DHA content and the infant's rate of increase in head circumference at 1 and 3 months.

Randomized Controlled Trials

DHA+EPA

Only one RCT on the effect of postnatal maternal interventions on growth patterns was identified for the current report. Lauritzen and colleagues (2005) randomized Danish breastfeeding women less than 2 weeks postpartum to olive oil or fish oil in the form of capsules, musli bars, and/or cookies, providing either 0.62 g/d EPA and 0.79 g/d DHA or 0.36 g/d EPA and 0.99 g/d DHA daily, depending on the dosage form. Of the 100 children completing the trial, 72 were followed up to 2.5 years. While growth in weight, length, and head circumference did not differ between the randomized groups up to 9 months, children in the fish oil group had larger BMI ($p = 0.022$), and head circumference ($p = 0.028$) than those in the olive oil group at 2.5 years (⁵⁴).

Observational studies

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study enrolled 244 mothers in the Netherlands. Concentrations by weight of total LCPUFAs, DHA, EPA, or ALA in breast milk samples provided by the mothers showed no significant associations with mean gain in weight, length, or BMI in the first year of life.⁹⁹

Combination of postnatal maternal and preterm infant interventions/exposures

The original review did not describe any interventions that combined both maternal and infant exposures.

Randomized Controlled Trials

DHA+EPA

The DINO study was an Australian RCT^{100, 101} that investigated the effect of both n-3 FA tuna oil supplements for lactating mothers of preterm (<33 weeks gestation) infants and formula supplemented with and without DHA from 2-5 days after delivery through the estimated due date ($n=657$). DHA supplementation had no observable effects on weight or head circumference at

4, 12, and 17 months, but DHA-supplemented infants were 0.7 cm (95% CI 0.1, 1.4 cm; $P=0.02$) longer in length at 18 months corrected age. An interaction effect was observed between DHA supplementation and birth weight strata for weight ($P=0.01$) and length ($P=0.04$). Infants who weighed ≥ 1250 g at birth and received supplemental DHA had greater length at 4 months corrected age and greater weight and length at 12 and 18 months corrected age.

Observational studies

No observational studies were identified with both maternal and preterm infant exposures.

Preterm infant interventions/exposures

The original review identified 20 RCTs, all of poor quality, that studied the effects of n-3 FA supplementation of preterm infants on postnatal growth patterns. Eighteen of the 20 studies found no effect on growth parameters at any time point. Two trials found that the n-3 FA-supplemented group actually had significantly lower weight at 6-18 months than the placebo-supplemented group. A meta-analysis in the original review of studies comparing formula with DHA+AA and control formula on mean weight and length at 4 months showed a non-significant effect (MWD for weight: -0.01, 95% CI -0.48, 0.47; MWD for length: -0.03, 95% CI -0.91, 0.86).

Randomized Controlled Trials

DHA+AA

Three studies examined differences in growth outcomes among preterm or VLBW infants supplemented with DHA and AA compared with controls.

Groh-Wargo compared 60 preterm infants in the U.S. given n-3 FA supplements (0.15%-0.24% DHA and 0.41% AA) to those given a placebo until one year corrected age. No significant differences were observed at any time point in weight, length, or head circumference. However, at 12 months corrected age, DHA+AA supplemented infants had significantly greater lean body mass ($p < 0.05$) and significantly less fat mass ($p < 0.05$) than the control infants.¹⁰²

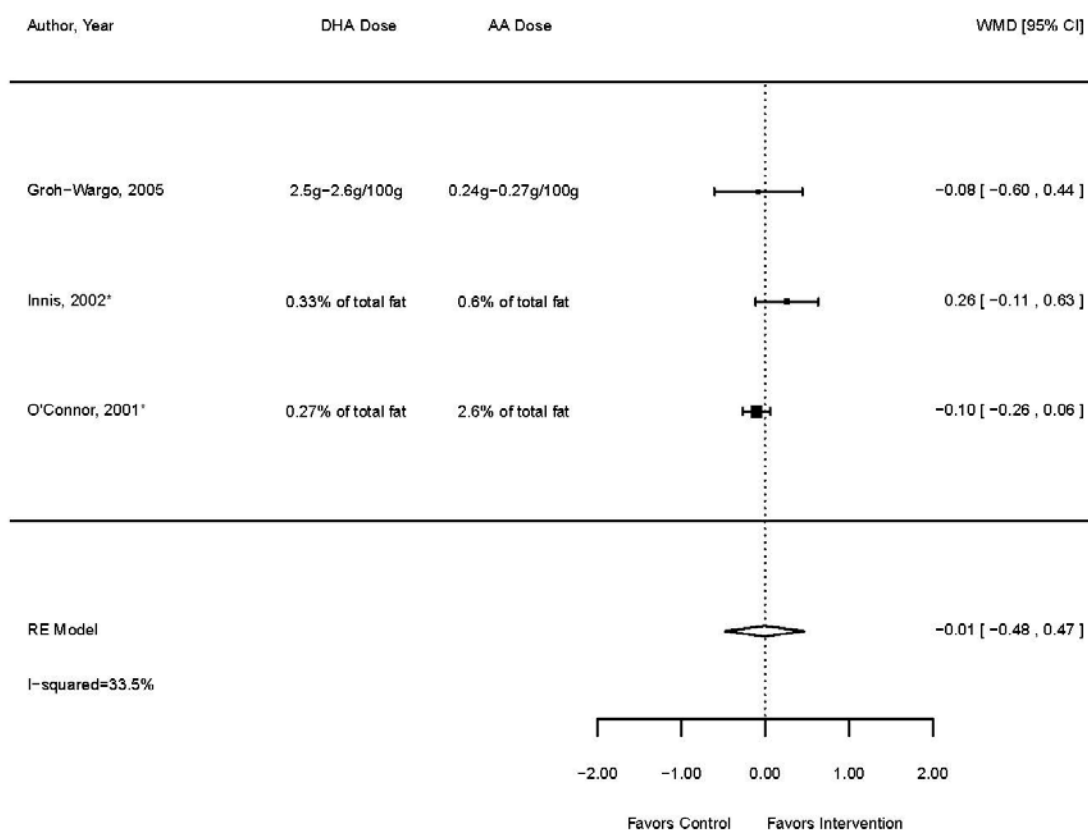
A study of 141 VLBW preterm infants in Norway supplemented with human milk with added oils containing DHA (6.9%) and AA (6.7%) from birth until discharge from the hospital (9 weeks on average) found no differences in growth outcomes between the groups at 6 months.¹⁰³

A study by Clandinin and colleagues (2005) of 361 preterm infants in the U.S. also compared the effects of administering two different kinds of DHA sources (algal sources and fish oil, both 0.32-0.33%) with AA (0.64-0.67%) from fungal sources with that of a placebo until 92 weeks postmenstrual age. Since the results were shown only on a graph, they were not abstracted into the evidence tables. However, the algal-DHA group was significantly greater than the control group in terms of weight (66 to 118 weeks) and length (48, 79, and 92 weeks). The algal-DHA group also exceeded the fish-DHA group in weight at 118 weeks PMA and in length at 57, 79, and 92 weeks PMA. Mean head circumference did not differ between the DHA groups and control groups at any follow-up time.¹⁰⁴

Results for the effects of DHA+AA compared to placebo on weight and length of preterm infants at 4 months were pooled¹⁰² with the outcomes of two studies from the original report, but the pooled effect sizes were not statistically significant (WMD [95% CI] in weight (kg): -0.01[-

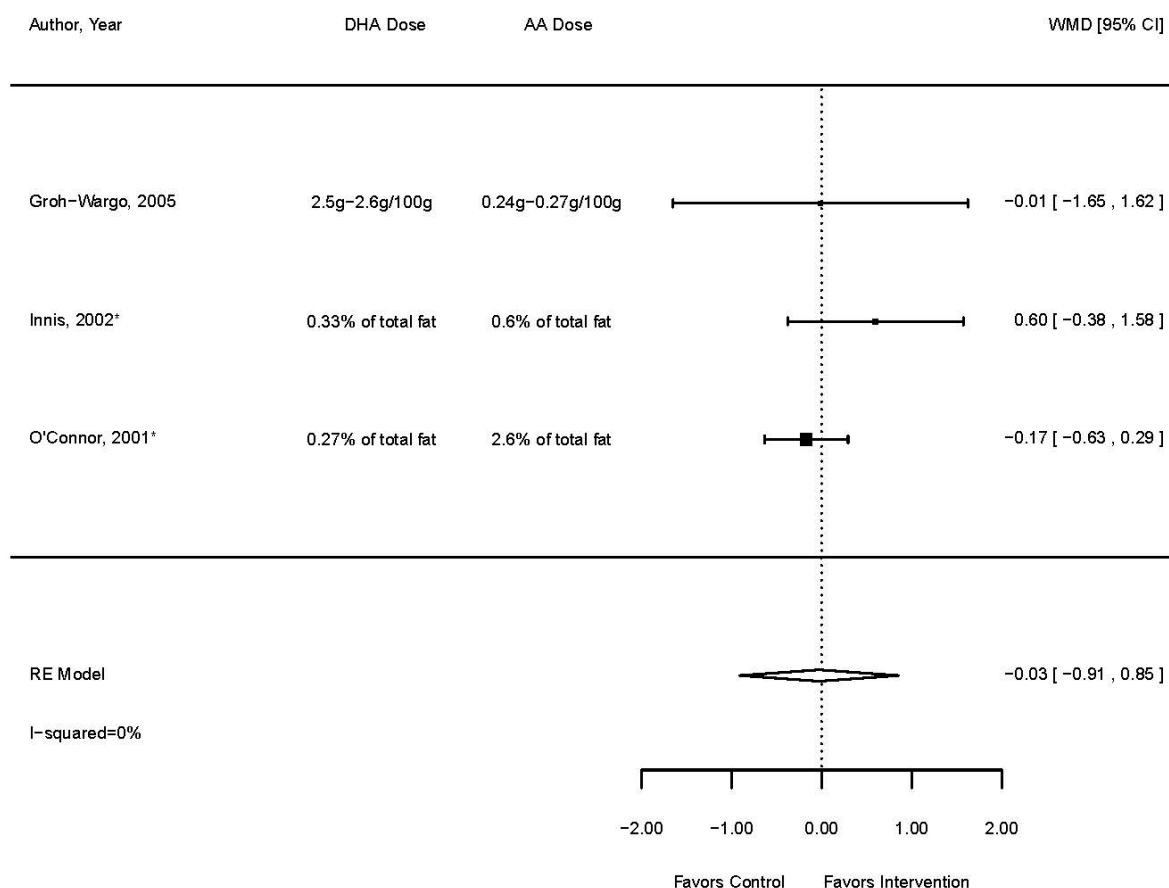
0.48, 0.47] $I^2=33.5\%$; WMD [95% CI] in length (cm): -0.03[-0.91, 0.85] $I^2=0\%$. The summary if this study and the results are shown in Table 11 and Figures 18 and 19.

Figure 18. Weight (kg) at 4 months – DHA + AA vs. placebo, given to preterm infants



* study from original report

Figure 19. Length (cm) at 4 months – DHA + AA vs. placebo, given to preterm infants



* study from original report

DHA+AA+EPA

Groh-Wargo compared the effects of n-3 FA supplements (0.16%-0.27% DHA, 0.43% AA, and 0.08% EPA) and placebo given to 60 U.S. preterm infants until one year corrected age. No significant differences were observed at any time point in weight, length, or head circumference (although at 12 months corrected age, DHA+AA+EPA-supplemented infants had significantly greater lean body mass ($p < 0.05$) and significantly less fat mass ($p < 0.05$) than the control infants).¹⁰²

A study of 139 preterm infants in the Netherlands supplemented with either preterm formula (0.14% DHA, 0.14% AA, and 0.039% EPA), term formula (0.07% DHA and 0.07% AA), or human milk found no significant differences in weight, length, or head circumference at 3 and 6 months corrected age.¹⁰⁵

Observational studies

No observational studies were identified for preterm infant exposures.

Term infant interventions/exposures

The original review identified 18 RCTs, all of good quality, that assessed the effect of n-3 FA supplementation in term infants on growth patterns. While the effects on growth patterns were not significantly different between study arms overall, certain timepoints and subgroups showed inconsistent differences. The meta-analysis showed a non-statistically significant overall effect of formulas containing DHA+AA at 4 months (MWD for weight: -0.06, 95% CI -0.45, 0.34; MWD for length: -0.33, 95% CI -1.07, 0.40) and 12 months (MWD for weight: -0.33, 95% CI -0.87, 0.21; mean weight difference for length: 0.37, 95% CI -1.26, 0.51; MWD for head circumference 0.14, 95% CI -0.83, 1.12). Similarly, formulas containing DHA showed a non-statistically significant overall effect at 4 months (MWD for weight: -0.12, 95% CI -0.44, 0.20, MWD for length: -0.43, 95% CI -1.20, 0.34; MWD for head circumference: 0.04, 95% CI -0.37, 0.46) and 12 months (MWD for weight: -0.33, 95% CI -0.87, 0.21; MWD for length: -0.71, 95% CI -2.18, 0.76; MWD for head circumference -0.04, 95% CI -0.45, 0.38). Four trials adjusted results for confounders, but failed to find any difference in the results.

Randomized Controlled Trials

DHA+AA

The current review identified five RCTs that studied the effect of DHA+AA supplementation in term infants.

Sala-Vila et al. (2004) compared growth outcomes in 35 term infants in Spain supplemented with human milk (0.4 and 0.3 g/100 g total FA as AA and DHA) to growth outcomes of infants supplemented with n-3 FA from eggs and to growth outcomes of infants supplemented with n-3 FA from fungi and algae (both 0.4 and 0.1 g/100 g total FA as AA and DHA). After three months supplementation, no differences in weight, length, or head circumference were observed.¹⁰⁶

Birch and colleagues (2005) randomized 103 term infants in the United States to DHA and AA (0.36% and 0.72% of total FA) from five days to 52 weeks. They observed no significant differences in weight, length, and head circumference at 6, 17, 39, or 52 weeks.¹⁰⁷ Since results were shown only graphically, they were not pooled.

Another study compared 30 term infants supplemented with term infant formula or a high DHA (0.20%) and AA (0.34%) formula for an unknown duration, commencing less than 14 days after birth. No significant differences were seen among either group at age 6 weeks or 2 years.¹⁰⁸

The BeMIM (Belgrade-Munch Infant Milk) Trial¹⁰⁹ recruited and randomized 213 infants to term infant formula or to a high DHA (7.2g/100mL) and AA (7.2g/100mL) formula from younger than 1 month to 4 months of life. While the rates of change of head circumference and weight gain were not statistically different between formula groups (high DHA+AA formula: 30.2 ± 6.3 vs. control formula: 28.3 ± 6.5 g/day, mean \pm SD, $P = 0.06$), rates of length gain were higher in the high DHA+AA group than in the term infant formula group (0.11 ± 0.02 vs. 0.10 ± 0.02 cm/day, $P = 0.02$).¹¹⁰

Observational studies

No observational studies were identified for term infant exposures.

Maternal and Infant Biomarkers

The original report included eleven studies on the relationship between n-3 FA biomarkers in children and growth patterns. Five were RCTs in preterm infants, five were RCTs in term infants, and one was a prospective cohort study of term infants. A negative correlation was seen between weight and the plasma or red blood cell content of DHA, and a positive correlation between weight and the content of AA in plasma or red blood cells was seen in some but not all studies. As biomarkers, n-6 FA (AA) may be related to infant weight gain, whereas DHA seems to be inversely related, but no significant clinical outcomes were detected.

The current report identified three additional studies with biomarker results related to growth patterns. A follow-up of studies on maternal n-3 FA supplementation during pregnancy and breastfeeding reviewed in the original report found no significant correlations between umbilical plasma phospholipid concentrations of LA, AA, ALA, DHA, or the ratio of n-3/n-6 fatty acids and the children's BMI at 7 years.⁸⁰ In addition, no significant correlations between umbilical plasma phospholipid concentrations of LA, AA, ALA, DHA, or the ratio of n-3/n-6 fatty acids at 4 weeks or 3 months and BMI at 7 years were found.

The DINO study¹⁰⁰ in preterm (<33 weeks gestation) infants in Australia (n=657) found no consistent relations between erythrocyte phospholipid polyunsaturated fatty acids and weight, length, and head circumference at 4 months corrected age. Changes in RBC-DHA were positively associated with gain in weight ($p<0.001$) and length ($p<0.001$) and negatively associated with gain in head circumference ($p<0.05$) between term and 6 months corrected age.

A study of 139 preterm infants in the Netherlands supplemented with preterm formula, term formula, or human milk found that changes in RBC-AA were positively associated with gain in head circumference ($p<0.001$) and negatively associated with gain in weight ($p<0.001$) and length ($p<0.05$), while changes in RBC-DHA/AA ratios were positively associated with weight gain ($p<0.001$) and length gain ($p<0.001$) but negatively associated with increases in head circumference ($p<0.001$) between term and six months corrected age. Changes in RBC-EPA showed no associations with gain in weight, length, or head circumference between term and six months corrected age.¹⁰⁵

Table 11. RCTs for Postnatal Growth Patterns

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Fleddermann et al., 2014¹⁰⁹</p> <p>Study name: BeMIM (Belgrade-Munch Infant Milk Trial)</p> <p>Study dates: Jan 2010 to May 2011</p> <p>Study design: Trial randomized parallel</p> <p>Location: Serbia</p> <p>Funding source / conflict: Industry</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 207 Infants completers 164</p> <p>Mother age: Control: 30.6 Intervention: 30.7 Breastfed: 30.1 (Control: 5.5 Intervention: 5.5 Breastfed: 4.7)</p> <p>Infant age: Gestation (weeks) Control: 39.2 Intervention: 39.2 Breastfed: 39.2 (Gestation (weeks) Control: 1.1 Intervention: 1.0 Breastfed: 1.1) until 28 days</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: Eligible infants had to be born apparently healthy from singleton pregnancies after 37-41 weeks of gestation, with a birth weight between the 3rd and 97th weight-for-age percentile according to the EURO-Growth charts.</p> <p>Exclusion Criteria: Infants with malformations, congenital heart defects, congenital vascular diseases, severe diseases of gastrointestinal tract, kidney, liver, central nervous system, or metabolic disease.</p>	<p>Start time: Infants within 28 days</p> <p>Duration: Infants until 120 days</p> <p>Arm 1: Control Formula (CF) Description Placebo/control formula Manufacturer HiPP GmbH & Co. Vertrieb KG (Pfaffenhofen, Germany) N-3 Composition. Blinding 600g cartons and labeled by random numbers. The products were packed in identical white boxes and labeled with the same product name. ALA 0.1g/100mL Arm 2: Intervention Formula (IF) Manufacturer HiPP GmbH & Co. Vertrieb KG (Pfaffenhofen, Germany) ALA 0.1g/100mL DHA 7.2g/100mL AA 7.2g/100mL Arm 3: Breastfed Description Breastfeeding reference group</p>	<p>Outcome head circumference gain Follow-up time days Arm 1 Sample size 82 mean 0.05 SD (0.01) Arm 2 Sample size 82 mean 0.05 SD (0.01) Outcome length gain Follow-up time days Arm 1 Sample size 82 mean 0.1 SD (0.02) Arm 2 Sample size 82 mean 0.11 SD (0.02) Outcome weight gain Follow-up time days Arm 1 Sample size 82 mean 28.3 SD (6.5) Arm 2 Sample size 82 mean 30.2 SD (6.3)</p>
<p>Collins et al., 2011¹⁰¹</p> <p>Study name: DINO</p> <p>Study dates: nr, DINO trial</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p>	<p>Study Population: Preterm infants Postpartum women Breast-feeding women</p> <p>Pregnant enrolled 545</p> <p>Infants enrolled 657 Infants completers 598</p> <p>Pregnant age: high DHA group 29.9; standard DHA group 30.2 (high DHA group 5.8; standard DHA group 5.4)</p> <p>Infant age: 4 day high</p>	<p>Inclusion Criteria: infant born <33 weeks gestation</p> <p>Exclusion Criteria: Infants were excluded if they had major congenital or chromosomal abnormalities; were a multiple birth where not all live births were eligible; were in other trials of fatty acid supplementation or had a lactating mother where tuna oil was</p>	<p>Start time: Infants birth</p> <p>Duration: NR</p> <p>Arm 1: standard DHA Description placebo soya oil capsules for lactating women and/or standard pre-term formula Manufacturer Capsule: Clover Corporation; Formula: Mead Johnson Nutritionals and Nutricia Australasia Dose 6*500mg placebo soya oil capsules Blinding All capsules were similar in size, shape and colour. Formula was packaged by colour code. Parents, clinicians and all research personnel were blinded to the participant's study group Arm 2: High DHA Description tuna oil capsules or DHA pre-term formula</p>	<p>Outcome head circumference Follow-up time 12 months Arm 1 Sample size 231 mean 46.2 SD (1.8) Arm 2 Sample size 225 mean 46.1 SD (1.8) Follow-up time 18 months Arm 1 Sample size 305 mean 47.8 SD (1.7) Arm 2 Sample size 282 mean 47.8 SD (1.8) Follow-up time 4 months Arm 1 Sample size 312 mean 41.8 SD (1.7) Arm 2 Sample size 289 mean 41.6 SD (1.7) Outcome length</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Follow-up: 18 months Follow-up article(s) ^{111, 112, 100, 113, 114}	DHA 3-6; standard 2-5 Race of Mother: NR (100)	contraindicated (bleeding disorders, anticoagulants).	Manufacturer Capsule: Clover Corporation; Formula: Mead Johnson Nutritionals and Nutricia Australasia Dose six 500 mg DHA-rich tuna oil capsules per day	Follow-up time 12 months Arm 1 Sample size 239 mean 74.1 SD (3.7) Arm 2 Sample size 226 mean 74.3 SD (3.6) Follow-up time 18 months Arm 1 Sample size 306 mean 81.2 SD (3.9) Arm 2 Sample size 286 mean 81.9 SD (4) Follow-up time 4 months Arm 1 Sample size 311 mean 61.2 SD (3.4) Arm 2 Sample size 294 mean 61.3 SD (3.2) Outcome weight Follow-up time 12 months Arm 1 Sample size 240 mean 9195 SD (1410) Arm 2 Sample size 231 mean 9317 SD (1455) Follow-up time 18 months Arm 1 Sample size 306 mean 10775 SD (1520) Arm 2 Sample size 292 mean 11029 SD (1764) Follow-up time 4 months Arm 1 Sample size 316 mean 6203 SD (1059) Arm 2 Sample size 299 mean 6218 SD (1013)
Smithers et al., 2008 ¹⁰⁰ Study name: DINO Study dates: 2001-2004 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Manufacturer supplied	Study Population: Preterm infants Lactating enrolled unclear Infants enrolled 143 Infants completers 125 Lactating enrolled unclear Mother age: Control: 31	Inclusion Criteria: infants born_x0001_33 wk gestation at the Women's and Children's Hospital of the Child, Youth, and Women's Health Service, Adelaide, Australia, between April 2001 and September 2003 Exclusion Criteria: Infants with major	Start time: Lactating approximately 5 days after birth Infants approximately 5 days after birth Duration: Lactating to estimated due date Infants to estimated due date Arm 1: Control group Description Placebo capsules and/or formula Active ingredients Linoleic acid 53.4% of fatty acids N-3 Composition. Dose 6 500-mg capsules per day to mothers Blinding The soy and tuna oil capsules were identical in size, color, and shape	duplicate data of id 8885

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
product Follow-up: 2 months, 4 months 4266, 7357 Follow-up article(s) ^{111, 112, 113, 101, 114}	Treatment: 29 (Control: 6 Treatment: 6) Infant age: 5 days (control) (mean gestational age at birth 29.4 weeks) 6 days (Treatment) (3) Race of Mother: NR (NR)	congenital or chromosomal abnormalities, lactating mothers for whom tuna oil was contraindicated (women with blood-thinning disorders or currently taking anticoagulants)	ALA 5.9% of total fatty acids Arm 2: Treatment Description DHA supplemented breastfeeding mothers and/or formula Active ingredients Linoleic acid 2.7% of fatty acids Dose 6 capsules or formula ad lib ALA 0.4% total FA DHA 29.5% total FA EPA 6.5% total FA AA 1.8% total FA	
Lauritzen et al., 2005 ⁵⁴ Study name: Danish National Birth Cohort Study dates: Recruitment: April 1999-February 2000 Follow-up 2.5 years Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Industry, Government Follow-up: 2.5 years Lauritzen 2004 Follow-up article(s) ^{44, 55}	Study Population: Breast-feeding women Infants enrolled 100 Infants completers 72 Mother age: High fish: 31.9 Fish oil: 29.6 Olive oil: 30.2 (High fish: 4.1 Fish oil: 4.3 Olive oil: 4.1) Race of Mother: NR (100%)	Inclusion Criteria: Pregnant women who were recruited for the Danish National Birth Cohort (DNBC) (16), all from the greater Copenhagen area, who were in their eighth month of gestation and had a fish intake below the median (0.40 g/d n-3LCPUFA) ... (554 women with a fish intake in the upper quartile (0.82 g/d n-3LCPUFA) were invited to participate in the study as a high fish intake reference group); uncomplicated pregnancy; body mass index (BMI) <30 kg/m ² ; no metabolic disorders; intention to breastfeed for at least 4 mo.; willingness to begin supplement within 2 weeks of birth. Newborns had to be healthy (no admission to a neonatal department), term (37–43 wk of gestation), singleton infants with	Start time: Lactating within 2 weeks of delivery Duration: Lactating 4 months Arm 1: Olive oil Description Control group receiving olive oil supplement Dose 2 musli bars daily; or 4 1000-mg capsules Blinding Investigators and families were blinded to the randomization throughout the first year of life of the infants. Fish oil as well as olive oil supplements were given as microencapsulated oils concealed in two müsli bars (produced by Halo Foods Ltd., Tywyn Gwynedd, Wales, UK) daily for the first 4 mo of lactation. Arm 2: Fish oil Description Intervention group receiving fish oil supplement Manufacturer BASF Health and Nutrition A/S, Ballerup, Denmark N-3 Composition 4.5g fish oil in 2 musli bars Dose 2 musli bars providing 0.62g EPA and 0.79g DHA; or fish oil capsules providing 0.36g EPA and 0.99g DHA DHA 0.79g/d EPA 0.62g/d Total N-3 1.5g/d Arm 3: High fish Description Group with high fish intake as reference group	Outcome bmi Follow-up time 2 months Arm 1 Sample size 51 mean 15.93 SD (1.37) Arm 2 Sample size 52 mean 15.74 SD (1.24) Arm 3 Sample size 50 mean 15.63 SD (1.36) Follow-up time 2.5 years Arm 1 Sample size 28 mean 15.86 SD (1.21) Arm 2 Sample size 42 mean 16.51 SD (1.08) Arm 3 Sample size 29 mean 16.11 SD (1.08) Follow-up time 4 months Arm 1 Sample size 46 mean 17.04 SD (1.7) Arm 2 Sample size 52 mean 16.93 SD (1.23) Arm 3 Sample size 49 mean 16.57 SD (1.66) Follow-up time 9 months Arm 1 Sample size 47 mean 17.64 SD (1.52) Arm 2 Sample size 53 mean 17.91 SD (1.24) Arm 3 Sample size 48 mean 17.27 SD (1.39) Outcome head circumference Follow-up time 1 week Arm 1 Sample size 56 mean 35.72 SD (1.53)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		<p>normal weight for gestation (17) and an Apgar score 7 at 5 min after delivery.</p> <p>Exclusion Criteria: NR</p>		<p>Arm 2 Sample size 54 mean 36.11 SD (1.25)</p> <p>Arm 3 Sample size 51 mean 36.18 SD (1.59)</p> <p>Follow-up time 2 months</p> <p>Arm 1 Sample size 50 mean 39.28 SD (1.16)</p> <p>Arm 2 Sample size 50 mean 39.7 SD (1.22)</p> <p>Arm 3 Sample size 47 mean 39.68 SD (1.27)</p> <p>Follow-up time 2.5 years</p> <p>Arm 1 Sample size 30 mean 49.74 SD (1.34)</p> <p>Arm 2 Sample size 41 mean 50.42 SD (1.2)</p> <p>Arm 3 Sample size 29 mean 50.62 SD (1.23)</p> <p>Follow-up time 4 months</p> <p>Arm 1 Sample size 46 mean 41.84 SD (1.12)</p> <p>Arm 2 Sample size 45 mean 42.17 SD (1.16)</p> <p>Arm 3 Sample size 45 mean 42.4 SD (1.38)</p> <p>Follow-up time 9 months</p> <p>Arm 1 Sample size 45 mean 45.29 SD (1.4)</p> <p>Arm 2 Sample size 52 mean 45.85 SD (1.53)</p> <p>Arm 3 Sample size 42 mean 45.81 SD (1.36)</p> <p>Outcome length</p> <p>Follow-up time 2 months</p> <p>Arm 1 Sample size 51 median 58.7 10th, 90th percentile (55.8, 61.3)</p> <p>Arm 2 Sample size 52 median 58.8 10th, 90th percentile (56.5, 61)</p> <p>Arm 3 Sample size 50 median 59.1 10th, 90th percentile (56.6, 60.9)</p> <p>Follow-up time 2.5 years</p> <p>Arm 1 Sample size 28 mean 92.65 SD (3.04)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				<p>Arm 2 Sample size 42 mean 92.58 SD (3.14)</p> <p>Arm 3 Sample size 29 mean 93.74 SD (2.93)</p> <p>Follow-up time 4 months</p> <p>Arm 1 Sample size 46 mean 64.02 SD (2.16)</p> <p>Arm 2 Sample size 52 mean 64.21 SD (2.08)</p> <p>Arm 3 Sample size 50 mean 64.7 SD (1.71)</p> <p>Follow-up time 9 months</p> <p>Arm 1 Sample size 47 mean 72.15 SD (2.04)</p> <p>Arm 2 Sample size 53 mean 72.66 SD (2.35)</p> <p>Arm 3 Sample size 48 mean 72.75 SD (2.01)</p> <p>Outcome weight</p> <p>Follow-up time 2 months</p> <p>Arm 1 Sample size 51 mean 5.4 10th, 90th percentile (4.77, 6.6)</p> <p>Arm 2 Sample size 53 median 5.5 10th, 90th percentile (4.7, 6.2)</p> <p>Arm 3 Sample size 50 median 5.3 10th, 90th percentile (4.9, 6.3)</p> <p>Follow-up time 2.5 years</p> <p>Arm 1 Sample size 30 mean 13.71 SD (1.26)</p> <p>Arm 2 Sample size 42 mean 14.16 SD (1.26)</p> <p>Arm 3 Sample size 29 mean 14.18 SD (1.43)</p> <p>Follow-up time 4 months</p> <p>Arm 1 Sample size 47 mean 7 SD (0.85)</p> <p>Arm 2 Sample size 53 mean 7 SD (0.73)</p> <p>Arm 3 Sample size 49 mean 6.93 SD (0.67)</p> <p>Follow-up time 9 months</p> <p>Arm 1 Sample size 47 mean 9.19 SD (0.94)</p> <p>Arm 2 Sample size 53 mean 9.47 SD (0.94)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 3 Sample size 48 mean 9.15 SD (0.9)
<p>Dunstan et al., 2008⁴²</p> <p>Study name: Dunstan</p> <p>Study dates: 2000-2003</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: NR</p> <p>Follow-up article(s) ^{56, 57, 58, 59}</p>	<p>Study Population: Healthy infants Pregnant women with allergies</p> <p>Pregnant enrolled 98 Pregnant completers 83</p> <p>Infants enrolled 83 Infants withdrawals 11 (7 FO, 4 control) Infants completers 72</p> <p>Pregnant age: Fish oil: 30.9 Control: 32.6 (Fish oil: 3.7 Control: 3.6)</p> <p>Infant age: Term (mean gestational period 275 days)</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: Healthy term infants of pregnant women enrolled in RCT of gestational supplementation</p> <p>Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected</p>	<p>Start time: Pregnant 20 weeks gestation</p> <p>Duration: Pregnant to term</p> <p>Arm 1: Control Description olive oil placebo Blinding capsules image matched Maternal conditions Current smoker 0% Maternal allergies 100%</p> <p>Arm 2: Fish oil Description same Manufacturer Ocean Nutrition, Halifax Nova Scotia Active ingredients 3-4mg/g vitamin E Viability none reported Dose 4 1-gm capsules fish oil per day Maternal conditions DHA 2.2 EPA 1.1 Current smoker 0% Maternal allergies 100% Other comment 1 fish oil supplying 2,2g/d DHA and 1.1g/day EPA</p>	<p>Outcome head circumference Follow-up time 30 months Arm 1 Sample size 36 mean 49.8 SD (1.7) Arm 2 Sample size 28 mean 49.4 SD (1.6) Outcome length Follow-up time 30 months Arm 1 Sample size 36 mean 93.3 SD (4.6) Arm 2 Sample size 28 mean 93.8 SD (3.8) Outcome weight Follow-up time 30 months Arm 1 Sample size 36 mean 14.1 SD (2) Arm 2 Sample size 28 mean 14.5 SD (2)</p>
<p>Goor et al., 2011⁶⁴</p> <p>Study name: Groningen LCPUFA study</p> <p>Study dates: 2004-2009</p> <p>Study design: Trial randomized parallel</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 18 months</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 119</p> <p>Infants enrolled 119 Infants completers 114</p> <p>Pregnant age: Placebo: 32.7 DHA: 32.5 DHA+AA: 32.9 (Placebo: 5.1 DHA: 4.4 DHA+AA: 4.8)</p> <p>Infant age: 18 months</p>	<p>Inclusion Criteria: women with a first or second low-risk singleton pregnancy, between the 14th and 20th weeks of pregnancy</p> <p>Exclusion Criteria: women with vegetarian or vegan diets; women with diabetes mellitus; birth complications</p>	<p>Start time: Pregnant 14th-20th week pregnancy Lactating 3 months after delivery Mothers 3 months after delivery Infants NR</p> <p>Duration: Pregnant NR Lactating 33-39 weeks Mothers 33-39 weeks Infants NR</p> <p>Arm 1: placebo Description Soy bean oil Brand name none</p> <p>Arm 2: DHA Description DHA plus soy bean oil Brand name Marinol D40 Manufacturer Lipid Nutrition B.V., Wormerveer, The Netherlands; AA: Dose 1 capsule DHA and 1 capsule soy bean oil</p>	<p>Outcome head circumference Follow-up time 18 months Arm 1 Sample size 34 mean 47.8 SD (1.5) Arm 2 Sample size 41 mean 47.6 SD (1.1) Arm 3 Sample size 39 mean 47.5 SD (1.4) Outcome length Follow-up time 18 months Arm 1 Sample size 34 mean 84 SD (3.8) Arm 2 Sample size 41 mean 82.8 SD (4.7) Arm 3 Sample size 39 mean 83.6 SD (2.9) Outcome weight Follow-up time 18 months Arm 1 Sample size 34 mean 11.5 SD (1.1) Arm 2 Sample size 41 mean 11.3 SD (1.4) Arm 3 Sample size 39 mean 11.5 SD (1.3)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
(multiple IDs) Follow-up article(s) ^{61, 62, 63, 65, 66, 67, 68, 35}	Race of Mother: NR (100)		once a day ALA 32 mg/d DHA 220 mg/d EPA 34 mg/d Arm 3: DHA+AA Description DHA plus AA Brand name AA: no brand name Manufacturer Wuhan Alking Bioengineering Co. Ltd., Wuhan, China Dose 2 capsules once a day ALA 7 mg/d DHA 220 mg/d EPA 36 mg/d AA 220 mg per capsule	
Hauner et al., 2012 ³⁶ Study name: INFAT Study dates: July 14 2006 - May 22 2009 Study design: Trial randomized parallel Location: Germany Funding source / conflict: Industry, Government Follow-up article(s) ^{69, 70, 71}	Study Population: Healthy pregnant women Pregnant enrolled 208 Pregnant withdrawals 38 Pregnant completers 170 Infants enrolled 188 Infants withdrawals 18 Infants completers 170 Pregnant age: 31.9 (4.9) 18-43 Race of Mother: NR (NR)	Inclusion Criteria: healthy pregnant women before the 15th wk of gestation, between 18 and 43 y of age, prepregnancy BMI (in kg/m ²) between 18 and 30, willingness to implement the dietary recommendations, sufficient German language skills. Exclusion Criteria: high-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity .4); hypertension; chronic diseases (eg, diabetes) or gastrointestinal disorders accompanied by maldigestion, malabsorption, or elevated energy and nutritional requirements (e.g., gluten enteropathy); known metabolic defects (eg, phenylketonuria);	Start time: Pregnant 15th wk of gestation Duration: Pregnant to 4 mo postpartum Arm 1: Control Description brief semistructured counseling on a healthy balanced diet according to the guidelines of the German Nutrition Society and were explicitly asked to refrain from taking fish oil or DHA supplements N-3 Composition. N-6 N-3 2.80 +- 1.17 (SD) at 32nd wk of gestation AA 10.15 +- 3.89 (SD) at 32nd wk of gestation Arm 2: Intervention Description Fish-oil supplement + nutritional counseling (to normalize the consumption of AA Brand name Marinol D-40 Manufacturer Lipid Nutrition DHA 1020 mg EPA 180 mg N-6 N-3 1.54 +- 0.63 (SD) at 32nd wk of gestation AA 8.82 +- 2.84 (SD) at 32nd wk of gestation Other comment 1 Vit E 9 mg	Outcome bmi Follow-up time 12 months Arm 1 Sample size 83 mean 16.7 SD (1.4) Arm 2 Sample size 87 mean 16.9 SD (1.5) Follow-up time 4 months Arm 1 Sample size 87 mean 16.2 SD (1.3) Arm 2 Sample size 87 mean 16.5 SD (1.4) Follow-up time 6 weeks Arm 1 Sample size 91 mean 15.3 SD (1.2) Arm 2 Sample size 89 mean 15.2 SD (1.4) Outcome head circumference Follow-up time 12 months Arm 1 Sample size 83 mean 46.1 SD (1.5) Arm 2 Sample size 87 mean 46.5 SD (1.6) Follow-up time 4 months Arm 1 Sample size 87 mean 41 SD (1.3) Arm 2 Sample size 87 mean 41.2 SD (1.3) Follow-up time 6 weeks Arm 1 Sample size 90 mean 38.8 SD (1.2) Arm 2 Sample size 89 mean 38.4 SD (1.1) Outcome length Follow-up time 12 months Arm 1 Sample size 83 mean 74.9 SD (2.8) Arm 2 Sample size 87 mean 75.5 SD (2.4) Follow-up time 4 months Arm 1 Sample size 87 mean 62.4 SD (2.2) Arm 2 Sample size 88 mean 62.6 SD (2) Follow-up time 6 weeks Arm 1 Sample size 91 mean 55.6 SD (2.6)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		psychiatric diseases; hyperemesis gravidarum; supplementation with n-3 LCPUFAs before randomization; and alcohol abuse and smoking.		<p>Arm 2 Sample size 89 mean 56 SD (2) Outcome weight Follow-up time 12 months Arm 1 Sample size 83 mean 9379 SD (1035) Arm 2 Sample size 87 mean 9650 SD (1025) Follow-up time 4 months Arm 1 Sample size 87 mean 6303 SD (724) Arm 2 Sample size 87 mean 6476 SD (679) Follow-up time 6 weeks Arm 1 Sample size 91 mean 4736 SD (625) Arm 2 Sample size 89 mean 4793 SD (606)</p>
<p>Birch et al., 2005¹⁰⁷</p> <p>Study name: NR</p> <p>Study dates: Not reported</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry, Government, Manufacturer supplied product</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 103 Infants completers 86</p> <p>Pregnant age: 31 years (4 years)</p> <p>Infant age: 3.6 _x0004_days (1.3 days) 1-5 days</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: All were born at 37– 40 wk after conception. Only singleton births with birth weight appropriate for gestational age</p> <p>Exclusion Criteria: Family history of milk protein allergy, genetic or familial eye disease, vegetarian or vegan maternal dietary patterns, maternal metabolic disease or infection, jaundice, perinatal asphyxia, meconium aspiration, or any perinatal event that resulted in placement of the infant in the neonatal intensive care unit.</p>	<p>Start time: Infants 1-5 days</p> <p>Duration: Infants 52 wks</p> <p>Arm 1: Control Description Commercial infant formula Brand name Enfamil with Iron Manufacturer Mead Johnson Nutritionals, Evansville, IN Active ingredients Linoleic acid-8.48g/L (14.6%); 14.7 g protein/L, 37.5 g fat/L, 69.0 g carbohydrate/L N-3 Composition. Blinding Each diet was masked by 2 color and 2 number codes, for a total of 4 possible diet assignments. The randomization schedule had random-length blocks (block length varied from 6 to 12) and was provided in individual sealed envelopes to the study site. ALA 1.5% of total fatty acids Arm 2: LCPUFA-supplemented formula Description Commercial formula supplemented with LCPUFA Brand name Enfamil with Iron plus DHASCO and ARASCO Manufacturer Formula: Mead Johnson; DHA+ARA: Martek Biosciences</p>	<p>data only reported on graph</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Active ingredients 15% linoleic acid, 14.7 g/L protein, 37.5 g/L fat, 69.0 g/L carbohydrate ALA 1.5% of total fatty acids DHA 0.36% of total fatty acids AA 0.72% of total fatty acids	
<p>Clandinin et al., 2005¹⁰⁴</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Trial randomized parallel</p> <p>Location: Canada</p> <p>Funding source / conflict: Industry</p>	<p>Study Population: Preterm infants</p> <p>Infants enrolled 361 preterm+105 term breastfed Infants completers 179 preterm and 76/105 term breastfed</p> <p>Infant age: 30.6 weeks postmenstrual age 24-36 weeks postmenstrual age</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Phase I: gestational age <35 weeks PMA and received <10 total days of enteral feedings of >30 mL/kg per day. Infants initially fed human milk were not enrolled unless formula was started within 10 days after completing the first day of human milk feeding Phase II: completion of phase I and ≥80% enteral intake from study formula during hospitalization and 100% of caloric intake from study formula at completion of phase 1. Birth weight<1500g</p> <p>Exclusion Criteria: congenital abnormalities of the gastrointestinal tract, hepatitis, hepatic or biliary pathology, necrotizing enterocolitis confirmed before enrollment, or history of underlying disease or congenital malformation likely to interfere with evaluation</p>	<p>Start time: Infants 10 days of age</p> <p>Duration: Infants 118 weeks</p> <p>Arm 1: Control Description Non-supplemented premature, discharge, and term formula Dose Ad lib Blinding Not reported Infant conditions Pre-term birth 119 (100%)</p> <p>Arm 2: Algal-DHA Description supplemented premature infant formula supplemented with DHA from algal oil Manufacturer Martek Biosciences Dose ad lib DHA 17mg/100kcal (0.33% by weight) EPA 0.1% by weight AA 34mg/100kcal (0.67% by weight)</p> <p>Arm 3: Fish-DHA Description Premature infant formula supplemented with DHA from tuna fish oil Manufacturer Martek Biosciences Dose ad lib DHA 17mg DHA/100 kcal AA 34mg/100 kcal</p> <p>Arm 4: Reference Description Breast fed term infants</p>	<p>data only reported on graph</p>
<p>Field et al., 2008¹⁰⁸</p> <p>Study name: NR</p>	<p>Study Population: Healthy infants</p>	<p>Inclusion Criteria: Inclusion criteria for all infants stipulated that by</p>	<p>Start time: Infants no later than 14 days</p> <p>Duration: NR</p>	<p>Outcome head circumference Follow-up time 6 wk Arm 1 Sample size 14 mean 38.6 SD (1.1)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study dates: NR</p> <p>Study design: Trial randomized parallel</p> <p>Location: Canada</p> <p>Funding source / conflict: Industry</p>	<p>Infants enrolled 30 Infants completers 30</p> <p>Infant age: 2 weeks 7 to 14 days</p> <p>Race of Mother: NR (100)</p>	<p>age 14 d infants were receiving 100 % of their intake by mouth from human milk or commercial infant formula and that infants were healthy with birth weight, length and head circumference between the 10th and 90th percentile for gestational age, according to the National Center for Health Statistics growth charts¹⁴.</p> <p>Exclusion Criteria: Infants with major congenital malformations, documented systemic or congenital infection, significant neonatal morbidity, diagnosed maternal autoimmune disorders, acute illness precluding oral feedings, or conditions requiring infant feedings other than standard formula or human milk were excluded from the study. None of the infants had received corticosteroids, erythrocyte or plasma transfusions, or intravenous lipid emulsions before entering the study</p>	<p>Arm 1: Formula (unsuppl) Description Placebo/control formula Brand name S-26 Manufacturer Wyeth Nutrition N-3 Composition. ALA 2.3% by weight</p> <p>Arm 2: Formula + LCP Description LCP supplemented formula Brand name S-26 Gold Manufacturer Wyeth Nutrition Active ingredients arachidonic acid - see below ALA 1.9% DHA 0.20% AA 0.34%</p> <p>Arm 3: Breastfed comparison Description Breastfed group, not randomized</p>	<p>Arm 2 Sample size 16 mean 38.4 SD (1.4) Arm 3 Sample size 16 mean 38.9 SD (1.2) Outcome length Follow-up time 6 wk Arm 1 Sample size 14 mean 56 SD (2) Arm 2 Sample size 16 mean 56 SD (2) Arm 3 Sample size 16 mean 58 SD (3) Outcome weight Follow-up time 6 wk Arm 1 Sample size 14 mean 4901 SD (590) Arm 2 Sample size 16 mean 5076 SD (646) Arm 3 Sample size 16 mean 5045 SD (516)</p>
<p>Groh-Wargo et al., 2005¹⁰²</p> <p>Study name: NR</p>	<p>Study Population: Preterm infants</p> <p>Infants enrolled 60</p>	<p>Inclusion Criteria: Preterm infants with birth weights from 750 to 1800 g and GA at birth <33 wk</p>	<p>Start time: Infants first enteral formula feeding</p> <p>Duration: Infants 24 kcal/fl oz formula until 40 wk corrected age; 22 kcal/fl oz formula from 40 wk CA</p>	<p>Outcome head circumference Follow-up time 12 months (corrected age) Arm 1 Sample size 14 mean 46.2 SE (0.4) Arm 2 Sample size 14 mean 46 SE (0.4)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study dates: sept 1997 - Sept 1998</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry, Government</p>	<p>Infants withdrawals 3 Infants completers 57</p> <p>Infant age: GA= 30 weeks (0.5) NR</p> <p>Race of Mother: NR</p>	<p>were recruited between September 1997 and September 1998 from the neonatal intensive care unit. No restrictions on the type of feeding before study entry.</p> <p>Exclusion Criteria: Congenital abnormalities that could affect growth or development, major surgery, periventricular hemorrhage greater than grade II (Papile classification), asphyxia resulting in severe and permanent neurologic damage, treatment with extracorporeal membrane oxygenation, maternal incapacity (including substance abuse), or uncontrolled systemic infection at the time of enrollment.</p>	<p>to 1 year CA</p> <p>Arm 1: Control Description Control formula without DHA or ARA Brand name Similac Special Care to 40 wk GA; and NeoSure until 1 year N-3 Composition. ALA 2.4 g/100 g (to 40 wk GA); 2.4 g/100 g (to 1 year) DHA 0 EPA 0 AA 0</p> <p>Arm 2: DHA+ARA (FF) Description DHA or ARA from fish/fungal oil Brand name Similac Special Care to 40 wk GA; and NeoSure until 1 year ALA 2.6 g/100 g (to 40 wk GA); 2.4 g/100 g (to 1 year) DHA 0.27 g/100 g (to 40 wk GA); 0.16 g/100 g (to 1 yr) EPA 0.08 g/100 g (to 40 wk GA); 0 (to 1 yr) AA 0.43 g/100 g (to 40 wk GA); 0 (to 1 yr)</p> <p>Arm 3: DHA+ARA (EF) Description DHA or ARA from egg-derived triglyceride and fish oil Brand name Similac Special Care to 40 wk GA; and NeoSure until 1 year ALA 2.5 g/100 g (to 40 wk GA); 2.4 g/100 g (to 1 year) DHA 0.24 g/100 g (to 40 wk GA); 0.15 g/100 g (to 1 yr) EPA 0 AA 0.41 g/100 g</p>	<p>Arm 3 Sample size 13 mean 46.2 SE (0.4) Follow-up time 35 weeks (corrected age) Arm 1 Sample size 18 mean 30.8 SE (0.2) Arm 2 Sample size 17 mean 30.6 SE (0.5) Arm 3 Sample size 18 mean 30.3 SE (0.4) Follow-up time 4 months (corrected age) Arm 1 Sample size 14 mean 41.9 SE (0.4) Arm 2 Sample size 16 mean 41.1 SE (0.6) Arm 3 Sample size 14 mean 42 SE (0.3) Follow-up time 40 weeks (corrected age) Arm 1 Sample size 18 mean 25.4 SE (0.3) Arm 2 Sample size 18 mean 34.5 SE (0.5) Arm 3 Sample size 17 mean 35 SE (0.3) Outcome length Follow-up time 12 months (corrected age) Arm 1 Sample size 14 mean 73.9 SE (0.9) Arm 2 Sample size 14 mean 75.2 SE (0.9) Arm 3 Sample size 13 mean 76.3 SE (0.8) Follow-up time 35 weeks (corrected age) Arm 1 Sample size 18 mean 42.5 SE (0.5) Arm 2 Sample size 17 mean 42.7 SE (0.7) Arm 3 Sample size 18 mean 42.7 SE (0.5) Follow-up time 4 months (corrected age) Arm 1 Sample size 14 mean 61.8 SE (0.7) Arm 2 Sample size 16 mean 60.9 SE (0.6) Arm 3 Sample size 14 mean 62.8 SE (0.7) Follow-up time 40 weeks (corrected age) Arm 1 Sample size 18 mean 48 SE (0.7) Arm 2 Sample size 18 mean 48.2 SE (0.7) Arm 3 Sample size 17 mean 48.1 SE (0.5) Outcome weight Follow-up time 12 months (corrected age) Arm 1 Sample size 14 mean 9343 SE (307) Arm 2 Sample size 14 mean 8977 SE (293) Arm 3 Sample size 13 mean 9505 SE (243) Follow-up time 35 weeks (corrected age) Arm 1 Sample size 18 mean 1916 SE (73) Arm 2 Sample size 17 mean 1871 SE (118) Arm 3 Sample size 18 mean 1874 SE (85)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				<p>Follow-up time 4 months (corrected age)</p> <p>Arm 1 Sample size 14 mean 6524 SE (220)</p> <p>Arm 2 Sample size 16 mean 6454 SE (212)</p> <p>Arm 3 Sample size 14 mean 6432 SE (217)</p> <p>Follow-up time 40 weeks (corrected age)</p> <p>Arm 1 Sample size 18 mean 3280 SE (135)</p> <p>Arm 2 Sample size 18 mean 3147 SE (149)</p> <p>Arm 3 Sample size 17 mean 3136 SE (105)</p>
<p>Helland et al., 2008⁸⁰</p> <p>Study name: NR</p> <p>Study dates: 1994-2003</p> <p>Study design: Trial randomized parallel</p> <p>Location: Norway</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: 7 years 6729, 10331: both in original report; and 10608 (biomarkers)</p> <p>Follow-up article(s) ^{52, 87, 88}</p>	<p>Study Population: Healthy infants Healthy pregnant women Breast-feeding women</p> <p>Infants enrolled 262 Infants completers 143</p> <p>Pregnant age: cod oil 28.6 n=175 corn oil 27.6 n=166 (cod oil 3.4; corn oil 3.2)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Healthy nulliparous or primiparous women, aged 19-35 with single pregnancies</p> <p>Exclusion Criteria: Unhealthy neonates</p>	<p>Start time: Pregnant week 18 of pregnancy</p> <p>Duration: NR</p> <p>Arm 1: Cod oil Manufacturer Peter Moller, Avd Orkla ASA, Oslo, Norway Active ingredients Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respective N-3 Composition. DHA 1183mg/10 mL EPA 803 mg/10mL Total N-3 2494 mg/10mL</p> <p>Arm 2: corn oil Active ingredients Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respective</p>	<p>Outcome bmi Follow-up time 7 years Arm 1 Sample size 61 mean 16.3 SD (1.7) Arm 2 Sample size 82 mean 16.4 SD (1.7)</p> <p>Outcome length Follow-up time 7 years Arm 1 Sample size 61 mean 128.6 SD (5) Arm 2 Sample size 82 mean 127.5 SD (5.5)</p> <p>Outcome weight Follow-up time 7 years Arm 1 Sample size 61 mean 27 SD (4.1) Arm 2 Sample size 82 mean 26.8 SD (4.1)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			ALA 92 mg/10mL	
Hoffman et al., 2008 ¹¹⁰ Study name: NR Study dates: nr Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Manufacturer supplied product	Study Population: Healthy infants Infants enrolled 244 Infants withdrawals 3 Infants completers 241 Infant age: 14 days Race of Mother: NR	Inclusion Criteria: 12–16 days of age, had a minimum birth weight of 2,500 g, and solely received formula at least 24 h prior to randomization Exclusion Criteria: history of underlying disease or malformation that could interfere with growth and development; large-for-gestational-age infants whose mothers were diabetic; breastfeeding within 24 h prior to randomization; evidence of formula intolerance or poor intake at time of randomization; weight at randomization less than 98% of birth weight; enlarged liver or spleen; or plans to move outside of the study area within the study time frame (120 days)	Start time: Infants 14 day Duration: NR Arm 1: Control Description soy formula without supplementation Brand name Enfamil ProSobee1, Mead Johnson & Company, Evansville, IN Blinding Aside from the addition of DHA and ARA, the formulas were identical in all other respects. Arm 2: DHA + ARA Description soy formula supplemented with a minimum 17 mg DHA/100kcal from algal oil and 34 mg ARA/100kcal from fungal oil Brand name Enfamil ProSobee1 LIPIL1, Mead Johnson & Company, Evansville, IN) DHA 0.3% AA 0.6%	Outcome head circumference Follow-up time 14-120d Arm 1 Sample size 86 mean gain 0.05 SE (1E-3) Arm 2 Sample size 93 mean gain 0.05 SE (1E-3) Outcome length Follow-up time 14-120d Arm 1 Sample size 86 mean change 0.1 SE (2E-3) Arm 2 Sample size 93 mean change 0.1 SE (2E-3) Outcome weight Follow-up time 14-120d Arm 1 Sample size 86 mean change 27.8 SE (0.8) Arm 2 Sample size 93 mean change 27.3 SE (0.7)
Lagemaat et al., 2011 ¹⁰⁵ Study name: NR Study dates: 2003 - 2006 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict:	Study Population: Preterm infants Low birth weight infants Infants enrolled 152 Infants completers 139 Infant age: Gestational age (week) PDF: 30.5 TF: 30.5 HM: 30.0 (PDF: 1.4 TF: 1.4 HM: 1.6)	Inclusion Criteria: infants born at gestational ages of 32 weeks or less and/or with birth weights of 1500 g or less Exclusion Criteria: NR	Start time: Infants at term Duration: Infants 6 months Arm 1: Term Formula (TF) Description Placebo/control formula Brand name Friso 1 normaal Manufacturer FrieslandCampina, Leeuwarden, The Netherlands N-3 Composition. Blinding NR ALA 63mg / 100ml	Outcome head circumference Follow-up time term age Arm 1 Sample size 41 mean 35.8 SD (1.5) Arm 2 Sample size 52 mean 35.9 SD (1.2) Arm 3 Sample size 46 mean 35.6 SD (1.5) Outcome length Follow-up time term age Arm 1 Sample size 41 mean 48.7 SD (2.1) Arm 2 Sample size 52 mean 48.7 SD (2.3) Arm 3 Sample size 46 mean 48.2 SD (2.5) Outcome weight Follow-up time term age

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Industry	Race of Mother: NR (100)		DHA 7mg / 100ml AA 7mg/ 100ml Arm 2: PDF Description Post-discharge formula (LCPUFA enriched) Brand name Friso 1 premature Manufacturer Friesland Foods ALA 59mg/ 100ml DHA 14mg/ 100ml EPA 3.9mg/ 100ml AA 14mg/ 100ml Arm 3: HM Description Human milk	Arm 1 Sample size 41 mean 3193 SD (489) Arm 2 Sample size 52 mean 3137 SD (511) Arm 3 Sample size 46 mean 3138 SD (513)
Lucia Bergmann et al., 2007 ⁴⁰ Study name: NR Study dates: 2000-2002 Study design: Trial randomized parallel Location: Germany Funding source / conflict: NR	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 144 Pregnant withdrawals 51 Pregnant completers 69 Pregnant age: 31 (DHA 4.69; control 4.89) Infant age: DHA 39.1; control 39.5 weeks (DHA 1.64; control 1.38) Race of Mother: White European (100)	Inclusion Criteria: at least 18 years of age and willing to breastfeed for at least three months were enrolled at 21 weeks' gestation during the period October 2000 to August 2002 Exclusion Criteria: increased risk of premature delivery or multiple pregnancy, allergy to cow milk protein, lactose intolerance, diabetes, smoking, consumption of alcohol (>20 g/week), or participation in another study. Infants excluded if they were premature at birth (<37 week gestation, or had any major malformations or hospitalized for more than one week.	Start time: Pregnant 21th week Duration: Pregnant 37th week Arm 1: Vitamins and minerals Manufacturer Nestle' (Vevey, Switzerland) Arm 2: Prebiotic Description basic supplement plus the prebiotic, fructooligosaccharide (FOS) (4.5 g) Manufacturer Nestle' (Vevey, Switzerland) Active ingredients fructooligosaccharide (FOS) (4.5 g) Arm 3: DHA Description basic supplement with FOS and DHA (200 mg) Manufacturer Nestle' (Vevey, Switzerland) Dose 200 mg DHA prepared from fish oil (assuming that some EPA but dose was not reported) DHA 200 mg EPA NR	Outcome bmi Follow-up time 1 month Arm 1 Sample size 74 mean 14.2 SE (0.37) Arm 3 Sample size 43 mean 14.06 SE (0.4) Follow-up time 21 months Arm 1 Sample size 74 mean 15.46 SE (0.32) Arm 3 Sample size 43 mean 14.7 SE (0.36) Follow-up time 3 months Arm 1 Sample size 74 mean 15.58 SE (0.38) Arm 3 Sample size 43 mean 16.14 SE (0.44) Outcome head circumference Follow-up time 1 month Arm 1 Sample size 74 mean 37.4 SE (0.41) Arm 3 Sample size 43 mean 37.1 SE (0.44) Follow-up time 21 months Arm 1 Sample size 74 mean 47.7 SE (0.36) Arm 3 Sample size 43 mean 48.4 SE (0.4) Follow-up time 3 months Arm 1 Sample size 74 mean 40.6 SE (0.43) Arm 3 Sample size 43 mean 40.6 SE (0.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				<p>Outcome length</p> <p>Follow-up time 1 month</p> <p>Arm 1 Sample size 74 mean 55.6 SE (0.64)</p> <p>Arm 3 Sample size 43 mean 56.3 SE (0.69)</p> <p>Follow-up time 21 months</p> <p>Arm 1 Sample size 74 mean 85.4 SE (0.56)</p> <p>Arm 3 Sample size 43 mean 85.5 SE (0.62)</p> <p>Follow-up time 3 months</p> <p>Arm 1 Sample size 74 mean 61.9 SE (0.65)</p> <p>Arm 3 Sample size 43 mean 61.7 SE (0.76)</p> <p>Outcome weight</p> <p>Follow-up time 1 month</p> <p>Arm 1 Sample size 74 mean 4.452 SE (0.23)</p> <p>Arm 3 Sample size 43 mean 4.516 SE (0.24)</p> <p>Follow-up time 21 months</p> <p>Arm 1 Sample size 74 mean 11.348 SE (0.2)</p> <p>Arm 3 Sample size 43 mean 10.747 SE (0.22)</p> <p>Follow-up time 3 months</p> <p>Arm 1 Sample size 74 mean 6.034 SE (0.23)</p> <p>Arm 3 Sample size 43 mean 6.19 SE (0.27)</p>
<p>Malcolm et al., 2003⁹⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Trial randomized parallel</p> <p>Location: NR</p>	<p>Study Population: NR</p> <p>Pregnant enrolled 100</p> <p>Pregnant withdrawals 37</p> <p>Pregnant completers 63</p> <p>Infants enrolled 60</p> <p>Infants withdrawals 5</p> <p>Infants completers 55</p> <p>Infant age: 279.6 (8.5)</p>	<p>Inclusion Criteria: d women who were expected to deliver their infants at term and planned to feed them on breast and/or formula milk</p> <p>Exclusion Criteria: diabetes, twin pregnancies, pre-</p>	<p>Start time: Pregnant week 15 Infants birth</p> <p>Duration: Pregnant birth</p> <p>Arm 1: Placebo</p> <p>Description contained 323 mg sunflower oil with high levels of oleic acid and was free of any significant amounts of LCPUFAs or their precursors</p> <p>Manufacturer R P Scherer Limited (Swindon, Wiltshire, UK)</p> <p>N-3 Composition.</p>	<p>Outcome head circumference</p> <p>Follow-up time 50 weeks PCA (postconceptional age)</p> <p>Arm 1 Sample size 27 mean 40.1 SD (2.3)</p> <p>Arm 2 Sample size 28 mean 39.9 SD (1.5)</p> <p>Follow-up time 66 weeks (post conceptional age)</p> <p>Arm 1 Sample size 27 mean 44.1 SD (1.7)</p> <p>Arm 2 Sample size 28 mean 43.8 SD (2.4)</p> <p>Outcome length</p> <p>Follow-up time 50 weeks PCA</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: NR	Race of Mother: NR (NR)	eclampsic toxemia, a past history of abruption or postpartum haemorrhage, allergy to fish products, a thrombophilic tendency, or who were receiving drugs that affect thrombocyte function (non-steroidal anti-inflammatories)	Dose 323 mg per capsule * 2 Blinding e identical in appearance and could not be identified on the basis of scent or taste Total N-3 0 Arm 2: DHA Description f a blended fish oil, Marinol D40, and contained 100 mg DHA in 323 mg oil per capsule Manufacturer R P Scherer Limited (Swindon, Wiltshire, UK) Dose 323 mg capsule * 2 DHA 200 mg EPA .64 mg (estimated based on the FA composition)	(postconceptional age) Arm 1 Sample size 27 mean 60.5 SD (2.9) Arm 2 Sample size 28 mean 60 SD (2.6) Follow-up time 66 weeks (post conceptional age) Arm 1 Sample size 27 mean 69.1 SD (3.2) Arm 2 Sample size 28 mean 68.5 SD (2.6) Outcome weight Follow-up time 50 weeks PCA (postconceptional age) Arm 1 Sample size 27 mean 5995.7 SD (827.9) Arm 2 Sample size 28 mean 5894.4 SD (662.3) Follow-up time 66 weeks (post conceptional age) Arm 1 Sample size 27 mean 8626.7 SD (208.2) Arm 2 Sample size 28 mean 8263.7 SD (999.4)
Sala-Vila et al., 2004 ¹⁰⁶ Study name: NR Study dates: nr Study design: Trial randomized parallel Location: Spain Funding source / conflict: Manufacturer supplied product	Study Population: Healthy infants Infants enrolled 35 Infants completers 35 Pregnant age: 28.3 Infant age: NR Race of Mother: NR (100)	Inclusion Criteria: full-term infants (37–42 wk gestation), of appropriate weight-for-gestation-age Exclusion Criteria: NR	Start time: Infants birth Duration: Infants 3 mo Arm 1: Human Milk (HM) Description breast milk with composition of protein carbohydrate fat ash Arm 2: E-PL formula Description E-PL formula provided 10% of its fat from egg PLs Brand name Ovotin 120, Lucas Meyer DHA 1.25% AA 1.9% Arm 3: S-TG formula Description single-cell (SC)-TG formula provided _x0004_0.3 and 0.5% of its fat from TGs synthesized by single cells of algal and fungal microorganisms Manufacturer Martek Biosciences DHA 0.1g/100g; 0.3% of 40-45% DHASCO AA 0.4g/100g, 0.5% of 38-44% ARASCO	Outcome head circumference Follow-up time 3 months Arm 1 Sample size 11 mean 41.86 SE (1.78) Arm 2 Sample size 12 mean 42.01 SE (1.46) Arm 3 Sample size 12 mean 43.98 SE (1.38) Outcome length Follow-up time 3 months Arm 1 Sample size 11 mean 60.5 SE (6.31) Arm 2 Sample size 12 mean 61.08 SE (5.31) Arm 3 Sample size 12 mean 60.98 SE (3.98) Outcome weight Follow-up time 3 months Arm 1 Sample size 11 mean 6460.1 SE (630.6) Arm 2 Sample size 12 mean 6640.8 SE (741) Arm 3 Sample size 12 mean 6491.9 SE

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(906.1)
<p>Stein et al., 2011³³</p> <p>Study name: NR</p> <p>Study dates: 02. 2005-02.2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: Mexico</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 1094 Pregnant completers 973</p> <p>Pregnant age: placebo 26.3; DHA 26.4 (placebo 4.6; DHA 4.9)</p> <p>Infant age: 39.1 (placebo 1.6; DHA 1.8)</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breast-fed for at least 3 mo, and to live in the area for at least 2 y after delivery</p> <p>Exclusion Criteria: NR</p>	<p>Start time: Pregnant 18-22 Gestinal week Infants birth</p> <p>Duration: Pregnant birth</p> <p>Arm 1: Placebo Description Olive oil Manufacturer Martek Biosciences Dose 2 capsules olive oil Blinding Similar in appearance and taste to DHA capsules Arm 2: DHA Description algal DHA capsules Manufacturer Martek Biosciences Dose 2 capsules * 200mg DHA 400 mg</p>	<p>Outcome head circumference Follow-up time 18 months Arm 1 Sample size 370 mean 47 SD (1.4) Arm 2 Sample size 369 mean 47 SD (1.5) Outcome length Follow-up time 18 months Arm 1 Sample size 370 mean 79.5 SD (2.8) Arm 2 Sample size 369 mean 79.6 SD (2.8) Outcome weight Follow-up time 18 months Arm 1 Sample size 370 mean 10.4 SD (1.2) Arm 2 Sample size 369 mean 10.4 SD (1.1)</p>
<p>Tofail et al., 2006⁸¹</p> <p>Study name: NR</p> <p>Study dates: enrollment January to March 2000</p> <p>Study design: Trial randomized parallel</p> <p>Location: Bangladesh</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 10 months</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 400 Pregnant completers 151</p> <p>Pregnant age: 22.7 years (4.35 years) NR</p> <p>Race of Mother: Asian (100%)</p>	<p>Inclusion Criteria: seems as if all pregnant women at 25 weeks gestation were enrolled, no inclusion criteria specified</p> <p>Exclusion Criteria: NR</p>	<p>Start time: Pregnant 25 weeks gestation</p> <p>Duration: Pregnant until birth</p> <p>Arm 1: placebo Description soy oil capsule N-3 Composition. Dose 4 one gram capsules per day Blinding capsules were identical in appearance Other dose 1 LNA 0.27 g Other dose 2 linoleic acid 2.25 g Arm 2: DHA supplement Description fish oil capsules Dose 4 one gram capsules per day DHA 1.2 g EPA 1.8 g</p>	<p>Outcome head circumference Follow-up time 10 months Arm 1 Sample size 124 mean 43.2 SD (1.4) Arm 2 Sample size 125 mean 43 SD (1.4)</p>
<p>Henriksen et al., 2008¹⁰³</p> <p>Study name: Unnamed Trial D</p> <p>Study dates: 2003-2006</p> <p>Study design: Trial</p>	<p>Study Population: Preterm infants</p> <p>Infants enrolled 141 Infants completers 129</p> <p>Mother age: Median: Intervention: 31 years</p>	<p>Inclusion Criteria: All VLBW infants (<1500g) born between December 2003 and November 2005 at Rikshospitalet-Radiumhospitalet Medical Center, Akershus University</p>	<p>Start time: Infants (intervention began when the infant received most of his nutrients enterally: >100ml human milk/kg body weight/day)</p> <p>Duration: Infants Until discharge or bottle of study oil was empty (average 63 days of age)</p> <p>Arm 1: Control</p>	<p>Outcome head circumference Follow-up time day 62 Arm 2 mean gain 1.2 SD (0.7) Follow-up time day 65 Arm 1 mean gain 1 SD (0.4)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>randomized parallel</p> <p>Location: Norway</p> <p>Funding source / conflict: Manufacturer supplied product</p> <p>Follow-up: 6 months{#11579}</p> <p>Follow-up article(s) ¹¹⁵</p>	<p>Control: 32 years 28-35 years</p> <p>Infant age: Median</p> <p>Gestational age: Control: 28.9 weeks Intervention: 28.4 weeks Gestational age: 26.6-30.9 weeks</p> <p>Race of Mother: White European (Intervention: 79%; Control 84%)</p>	<p>Hospital, Buskerud Hospital, and Vestfold Hospital in Norway</p> <p>Exclusion Criteria: Major congenital abnormalities or cerebral hemorrhage (grade 3 or 4, as determined through ultrasonography)</p>	<p>Description Study oil: soy oil and medium chain triglycerides</p> <p>Active ingredients 127mg linolenic acid/100 ml milk(27.1% total fatty acids)</p> <p>N-3 Composition.</p> <p>Dose 0.5 ml study oil/100 ml human milk</p> <p>Blinding Study oils packed in numbered bottles in hospital pharmacy</p> <p>ALA 16mg/100 ml milk; 3.4% total fatty acids</p> <p>Arm 2: Intervention</p> <p>Description DHA and AA-containing oil</p> <p>Manufacturer Martek Biosciences</p> <p>Active ingredients 88mg/100 ml linoleic acid per 100 ml milk (18.8%)</p> <p>Dose 0.5 ml study oil per 100 ml milk, ad lib</p> <p>Maternal conditions</p> <p>Infant conditions</p> <p>DHA 32mg/100ml milk (6.9%)</p> <p>AA 31 mg/100 ml milk (6.7% total fatty acids)</p> <p>Current smoker 22% during pregnancy</p>	

Table 12. Observational Studies for Postnatal Growth Patterns

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Much, et al., 2013⁷⁰</p> <p>Study name: INFAT</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Germany</p> <p>Funding source / conflict: Industry, Government, Some authors employed by industry (companies that make the supplements)</p> <p>Follow-up article(s) ⁶⁹, ⁷¹, ³⁶</p>	<p>Study Population: Healthy infants Breast-feeding women</p> <p>Pregnant enrolled 208</p> <p>Lactating enrolled 152/120</p> <p>Infants enrolled 56/31</p> <p>Lactating enrolled 152/120</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: Healthy pregnant women around 14th week of gestation</p> <p>Exclusion Criteria: none reported</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Much, et al., 2013⁷¹</p> <p>Study name: INFAT</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Germany</p> <p>Funding source / conflict: Industry, Government, Some authors employed by industry (companies that make the supplements), Multiple foundations and Societies, None</p> <p>Follow-up article(s) ^{69, 70, 36}</p>	<p>Study Population: Healthy infants Breast-feeding women</p> <p>Pregnant enrolled 208</p> <p>Infants completers 187</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: Healthy pregnant women at 14th week of gestation</p> <p>Exclusion Criteria: None reported</p>
<p>Scholtens, et al., 2009⁹⁹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government, Multiple foundations and Societies, None</p>	<p>Study Population: NR</p> <p>Pregnant enrolled 4146</p> <p>Infants enrolled 276 Infants completers 244</p> <p>Infant age: 0</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: Children of mothers recruited from the general population during pregnancy</p> <p>Exclusion Criteria: None reported</p>

Neurological Development

Key Findings and Strength of Evidence

Antepartum supplementation:

- The original report identified one study that supplemented pregnant women with fish oil and found no effects on infant EEG.
- The current report identified one large RCT that reported no effects of DHA on brain auditory evoked potentials despite low baseline intakes; one small RCT on sleep patterns that reported significant effect on arousal at days 1 and 2 but no other findings among any of the many other measures; and two large RCTs of fish oil that found no differences in motor development at 10 or 18 months.
- The current report identified two prospective cohort studies and three biomarker studies. One prospective cohort study found an association between the lowest quintile of n-3FA and risk for epilepsy; one prospective cohort study found no association of n-3, n-6, or n-6/n-3 FA with a measure of fine motor development. One biomarker study found no association of any maternal n-3 or n-6 FA biomarkers and Bailey motor development. A second study found an inverse association of videographically assessed (mildly abnormal) movement at 3 months with arterial but not venous cord blood biomarkers; at 18 months, the same cohort showed an association of umbilical vein DHA with NOS but not PDI; umbilical arterial LC-PUFA were no longer associated with any neurodevelopmental indices. A third study found no significant association of umbilical DHA or AA and Maastricht motor scores at 7 years of age.

Pre and postpartum maternal supplementation

- One RCT that compared DHA vs DA+AA vs placebo had inconsistent effects on mildly abnormal movement and PDI at 0.5, 3, and 18 months. Maternal biomarkers showed inconsistent associations with infant movement.

Postpartum maternal supplementation and infant outcomes:

- Healthy term infants breastfed by mothers who received supplemental DHA showed significantly improved adjusted PDI scores at 30 months but not at 12 months. At 5 years a different battery of age-appropriate motor tests showed no difference between groups.

Postpartum supplementation of preterm infants

- The original report identified six RCTs that could not be pooled and reported mixed findings. The current report identified three RCTs that could not be pooled due to different interventions, outcome measures, and followup times; supplementation showed mixed effects.

Postpartum infant supplementation healthy term

- The original report identified seven RCTs with mixed interventions, durations, and outcome measures; pooling three RCTs of DHA+AA showed no effect on PDI at 12 months compared with placebo. The current report identified three RCTs. In a small Turkish study, DHA-supplemented formula improved brainstem maturation at 4 months.

In a large Italian study, DHA affected only one out of four measures of gross motor development at 12 months. One larger Dutch study showed significant impact of DHA+AA on mildly abnormal movement at 2 months compared with placebo; at 18 months, intervention, placebo, and breastfed children had similar PDI scores; at 9 years, the fine motor control of both supplemented and placebo children was similar but poorer than that of breastfed.

Description of Included Studies

We identified eleven RCTs and five large observational studies that assessed the effects of n-3 FA interventions on, or the associations of n-3 FA exposures with, neurodevelopment in the developing infant and child, as distinct from cognitive development. Outcomes varied and included the Bailey's Psychomotor Development Index (PDI), brainstem auditory evoked potentials, neurological optimality scores, general movement assessment, and the Touwen Neurological Assessment, among others.

This section reports the findings of studies that assessed the effects of prenatal, postnatal maternal (breast milk), or postnatal infant PUFA supplementation or exposure on these outcomes. Studies identified for this report are summarized in Table X and briefly summarized below.

Antepartum Maternal Supplementation with or Exposure to n-3 Fatty Acids and Infant Neurodevelopmental Outcomes

Randomized Controlled Trials

The original report identified one RCT that assessed the effects of an n-3 intervention (cod liver oil) with pregnant women on neurodevelopmental outcomes; the outcome was brain maturity as assessed by infant electroencephalogram (EEG) recordings at 1 day and again at 6 months of age; this study found no effect of maternal supplementation at either time point. No studies were identified for the current report that assessed effects of maternal supplementation on infant EEG patterns.

For the current report, we identified four RCTs that assessed the effects of antepartum maternal supplementation with n-3 FA on neurodevelopmental outcomes. We also identified three articles that reported the results of three prospective cohort studies assessing the association between antepartum maternal n-3 FA exposures and infant neurodevelopment.

DHA vs. placebo

Brainstem Auditory Evoked Potentials. For the current report, we identified one 2012 RCT that randomized 1,094 pregnant women in Mexico to 0.4g/d algal DHA or corn and soy bean oil from approximately 17 weeks of gestation through term and assessed the effect of supplementation on brainstem auditory evoked potentials (a measure of brainstem maturation).³² The women had low baseline intakes of DHA. No differences were seen in any comparisons (latency and interpeak latency at 1, 3, and 5 milliseconds) between infants of placebo and DHA-supplemented women at either time point.

Sleep/Wakefulness. A 2013 RCT randomized 48 U.S. women to consume five cereal bars per week from 24 weeks of gestation until delivery; 27 of the women received bars that contained 0.3g DHA each (for an average of 0.21g/d DHA and a trace amount [0.023 g/d] EPA) and the

remaining women received bars without DHA.³⁹ Early infant sleep patterns, a predictor of subsequent neurological development, were measured at 1 and 2 postnatal days using a pressure sensitive mattress. On both days 1 and 2, infants of DHA-supplemented mothers showed fewer arousals in both quiet (adjusted $p=0.006$ for day 1, adjusted $p=0.011$ for day 2) and active (adjusted $p=0.012$ for day 1) sleep than did infants of control mothers. No differences were observed between groups in arousal from active sleep on day 2, quiet sleep, sleep transitions, active sleep, wakefulness, sleep bout lengths, mean sleep period, and longest sleep period.

Fish Oil vs. Placebo

Bailey's PDI or Motor Standardized Score. For the current report, we identified two studies that assessed the effects of supplementing pregnant women with fish oil on infant psychomotor development, compared with those of placebo.^{34, 81}

In one 2006 study, four hundred healthy pregnant women in Dhaka Bangladesh were randomized to receive fish oil (1.2g/d DHA and 1.8g/d EPA) or placebo (soy oil) from the 25th week of gestation through term. No differences were seen in PDI scores between the two groups of infants ($n=249$) at 10 months of age (effect size $-2.1\pm1.1[-4.3, 0.1]$).

A 2010 study, the DOMInO Study,³⁴ randomized 2,399 women seen at five hospitals in Australia to a daily DHA-rich fish oil supplement (0.8g/d DHA; 0.1g/d EPA) or placebo beginning at 21 weeks of gestation or earlier through term. The primary outcome of the study was risk for depression; however infant neuro- and cognitive development were assessed as secondary outcomes in 726 infants at 18 months of age. No differences were seen in unadjusted or adjusted effect sizes among boys or girls between treatment group offspring ($(-0.69[-2.31, 0.93]p=0.40)$ for girls; $(0.85[-1.00, 2.70]p=0.37)$).

Observational Studies

We identified two prospective cohort studies that assessed the association between maternal intakes of n-3 FA during pregnancy and infant neurodevelopmental outcomes.^{116, 117} We also identified three studies (reported in four publications) that assessed the association between umbilical venous LC-PUFA and these outcomes (one of these studies was a followup to a study described in the original report, and another was a followup to a study described below).

Prospective Cohort Studies

A 2010 study used data from the Danish National Birth Cohort, which estimated n-3 FA intake from self-administered FFQ around 25 weeks gestation.¹¹⁶ The authors followed 65,754 live-born infants up to 11 years of age to determine their risk for a diagnosis of epilepsy (according to ICD-10 criteria) associated with quintiles of total n-3 FA intake. Based on the middle quintile as the reference (0.31 ± 0.07 g/d, adjusted for energy intake), infants born to women with the lowest quintile of pregnancy n-3FA intake (0.12 ± 0.04 g/d) were at nonsignificantly increased risk for epilepsy (adjusted incidence rate ratio, $1.28[0.98, 1.67]$) and infants born to women with the highest quintile (0.82 ± 0.35 g/d) of intake were at a significantly increased risk for epilepsy (IRR $1.33[1.02, 1.74]$). Restricting the analyses to children for whom information on breastfeeding was actually available, the nonsignificant risk increase remained for the lowest quintile of n-3FA intake (IRR $1.35[0.99, 1.83]$), and the risk for infants of mothers with the highest quintile of intake was no longer significant (IRR $1.24[0.90, 1.69]$).

A 2013 study assessed the association between n-3 FA/ n-6 FA intake during pregnancy among 1,335 French women enrolled in the EDEN cohort study and performance of their

children at 2 years of age on tests of cognitive and motor development, included the Peg Movement Task (PMT)-5.¹¹⁷ Neither breastfed nor never-breastfed children showed any association between performance on the PMT-5 and maternal intake of n-6 FA, n-3 FA or the n-6/n-3 ratio.

Biomarker Studies

A 2013 study whose primary outcome of interest was the association between prenatal mercury exposure, LC-PUFA, and infant neurodevelopment assessed the association between maternal serum n-3 and n-6 FA and Bailey Scale of Infant Development composite motor scores at 18 months of age among a population-based cohort of 606 mother-child pairs in Italy.¹¹⁸ No significant association was found between motor scores and maternal EPA, DHA, ALA, DPA, or AA status or n-6:n-3 ratio.

Bouwstra and colleagues utilized a cohort of children enrolled in a RCT to assess the effect of DHA and AA-supplemented infant formula (compared with standard formula and breast milk) on neurological development to assess the associations between umbilical venous and arterial n-3FA status and neurological development at 3 months⁶⁷ (the RCT is described below). Neurological development was assessed by videographically recording and analyzing general movement quality: Movements were classified as normal optimal, normal suboptimal (both normal optimal and normal suboptimal are considered clinically normal), mildly abnormal or definitely abnormal. At 3 months, the quality of general movements among 269 infants was not associated with the DHA or AA concentration of venous cord blood. However movement quality was associated with the FA content of arterial cord blood. An increase in mildly abnormal movements was associated with adjusted lower arterial cord blood levels of total monounsaturated FA; several n-6 FA, including AA; n-9 FA; and total n-3 and n-6 FA.

Bouwstra and colleagues reassessed neurologic development of the same cohort at 18 months (n=317), this time using the Hempel neurological exam to obtain a neurologic optimality score (NOS) and the Bailey PDI. Children whose umbilical vein DHA concentrations were in the lowest quartile had significantly lower adjusted NOS but no difference in PDI scores compared with children whose umbilical vein DHA concentrations were higher ($\beta=0.17$; $p=0.003$). Umbilical venous AA concentrations were not associated with NOS or PDI scores in multivariate analysis, and umbilical arterial LC-PUFA concentrations were not associated with neurodevelopmental indices.

In a followup to a 2003 cohort study described in the original report (but not originally including neurological outcomes), Bakker and colleagues also assessed the association between umbilical venous LC-PUFA and neurological development, as indicated by motor development, in another Dutch cohort.¹¹⁹ The cohort comprised 750 white children born between 1990 and 1994 and seen at the University Hospital Maastricht, for whom umbilical blood LC-PUFA had been assessed. At 7 years of age, 306 children were given the Maastricht Motor Test (MMT) by a blinded tester. The composite (total) score comprises a quantity score (whether the participant can perform the movement) and a quality score (how well the participant performs the movement). MMT total score and quality score were significantly positively associated with umbilical plasma DHA in multivariate models ($\beta=0.13$, $p=0.01$; $\beta=0.14$, $p=0.10$, respectively). Umbilical DHA was not significantly associated with MMT quantity score. Umbilical AA was non-significantly negatively associated with MMT scores ($(\beta=-0.10, p=0.069; \beta=-0.11, p=0.052,$ for total and quality scores, respectively).

Ante- and Postpartum Maternal Supplementation with n-3 FA and Infant Neurodevelopment

For the current report, we identified one study that examined the effects of both prenatal and postnatal maternal supplementation with LCPUFA on infant neurological development.

DHA or DHA plus AA vs. Placebo

For the current report, we identified one study, reported in two publications, that examined the effects of both prenatal and postnatal maternal supplementation with DHA or DHA plus AA on infant neurological development compared with those of placebo.

One study, reported in two publications, enrolled 183 healthy pregnant women between 14 and 20 weeks of pregnancy (80% between 15.6 and 17.4 weeks) in the Netherlands and randomized them to receive a daily supplement of vitamins and minerals alone, vitamins and minerals along with DHA (0.22 g/d), or vitamins and minerals along with DHA (0.22g/d from fish oil) and AA (0.22g/d) from enrollment to 3 weeks after delivery.³⁵ Infant neurological development was assessed at 0.5 months, 3 months,³⁵ and 18 months⁶⁴ of age using two instruments. At 0.5 months and 18 months, a standard neurological assessment was conducted, resulting in a NOS. At all time points, general movement quality was assessed videographically as described above. And at 18 months, infants were assessed using the PDI. No significant differences in NOS were seen among the three groups of infants at 0.5 months of age (n=183). At 0.5 months of age, infants of mothers supplemented only with DHA showed significantly more mildly abnormal movements than the infants of control mothers (adjusted β 3.867, $p=0.021$) and non-significantly more than those who received DHA plus AA (adjusted β , $p=0.19$), and controls did not differ from the DHA plus AA group ($p=0.29$). At 3 months (n=96), the adjusted differences attained significance for DHA vs. controls ($p=0.014$), and for DHA vs. DHA plus AA ($p=0.017$). At 18 months (n=114), no difference in PDI scores was observed among the three groups of infants.⁶⁴

Maternal Biomarkers

The study by van Goor that assessed the effects of maternal pre- and postnatal supplementation with DHA or DHA plus AA on neurological development also assessed the association between maternal³⁵ biomarkers of n-3 FA status and infant neurological development. They reported no correlations between prenatal (3 weeks gestation) maternal erythrocyte n-3, n-6 FA, or the DHA:AA ratio and the NOS. Mildly abnormal infant general movements at 2 weeks were correlated with lower maternal erythrocyte AA compared with normal general movements (median 12.25 vs. 13.03, $p=0.02$). No associations were found at 3 months.³⁵

Postpartum Maternal Supplementation with n-3 FA and Infant Neurodevelopment

For the current report, we identified one new RCT, reported in two publications, that examined the effects of supplementing lactating mothers with n-3 FA on infant neurological development.

DHA vs. Placebo

We identified two new articles reporting on one RCT that examined the effects of postpartum maternal DHA supplementation on infant neurological development.^{120, 121}

Jensen and colleagues randomly assigned 227 pregnant U.S. women who planned to breastfeed for at least 4 months to either algal DHA (approximately 0.2g/d) or placebo, to begin at 5 days postpartum and continue for 4 months.¹²⁰ Mothers of preterm or low birth weight infants were excluded. Compliance with the supplement was 95 percent to 100 percent. The Bailey PDI and the Gesell Developmental Inventory were used to assess motor development at 12 and 30 months of age in the 230 infants (including 3 twin pairs). At 12 months, no differences were seen between groups in either of the tests. At 30 months, infants of DHA-supplemented mothers had significantly higher adjusted PDI scores than infants of placebo-supplemented mothers ($p=0.0008$), although no difference was seen using the Gesell Inventory.¹²¹

A subsequent article reported on psychomotor development as measured by the K-ABC Hand movement scale; McCarthy Leg Coordination component; Purdue Peg board Test; and the Developmental Test of Visual Motor Integration Motor component at 5 years of age in the same population ($n=60$ children of DHA-supplemented mothers and 57 children of placebo mothers).¹²⁰ No differences were seen between the two groups of infants in performance on any of the tests.

Maternal and Infant Biomarkers

Jensen and colleagues assessed the association between infant plasma phospholipid DHA and psychomotor development and found no association (data not reported).¹²¹

Infant Formula Supplementation with n-3 FA and Neurodevelopment in Preterm Infants

The original report identified six RCTs that examined the effects of supplementing formula with n-3 FA with or without breast feeding on neurological development among preterm infants; the studies dated from 1999 to 2004. Duration of supplementation varied. Followups ranged from 1 month to 24 months: in some studies, the intervention ended several months before followup assessment. Three RCTs assessed the use of formula supplemented with DHA plus AA, two RCTs assessed the use of formula supplemented with DHA plus EPA plus AA, and one used DHA plus gamma-linoleic acid. Across the studies, outcomes were mixed: two studies reported a positive effect of DHA plus AA on PDI scores, whereas four reported no or negative effects. No studies were pooled because of differences in intervention duration and followup.

DHA, DHA plus AA, or DHA plus EPA vs. Placebo

Three RCTs were identified for the current report that assessed the effects of providing infant formula supplemented with DHA with or without EPA and AA on PDI scores of preterm infants. The outcomes could not be pooled because of differences in the interventions and followup times.

A 2005 RCT randomized 27 preterm infants in Taiwan (born at 30 to 37 weeks gestation and over 2kg body weight) to oral formula supplemented with DHA (0.05%) and AA (0.1%) or a control formula for 6 months. PDI scores were non-significantly higher in the supplemented group at 6 months (102.2 ± 10.5 vs. 95.4 ± 13.2) and significantly higher in this group at 12 months (98.0 ± 5.8 vs. 86.7 ± 11.1 , $p=0.008$) compared to the unsupplemented group.

Another 2005 RCT randomized 361 preterm U.S. infants (≤ 35 weeks gestation) to one of three groups: oral formula supplemented with algal DHA (0.017g/100kcal) plus algal AA (0.034g/100kcal); oral formula supplemented with fish DHA and algal AA in the same concentrations; or standard formula for approximately 18 months (until 118 weeks postmenstrual age [PMA]).¹⁰⁴ At 118 weeks PMA, both supplemented groups had significantly higher PDI

scores than the unsupplemented group but significantly lower than a group of term breastfed infants of similar ages.

The DINO trial, a 2009 RCT, randomized 657 preterm infants (≤ 33 weeks gestation) to receive “high DHA” (1% of total fatty acids) or “standard DHA” (0.3% of total fatty acids) enteral formula from day 2 to 4 until term-corrected age and assessed the effects of the two supplements at 18 months corrected age on a number of outcomes, including neurological development. In an intention to treat analysis, the authors reported no differences between groups in PDI scores.¹¹³

Infant Formula Supplementation with n-3 FA and Neurodevelopment in Term Infants

The original report identified seven RCTs that examined the effects of supplementing infant formula with various combinations of n-3 and n-6 FA on neurodevelopmental outcomes of term infants. Across these RCTs, effects of supplementation on neurodevelopment, usually assessed using the Bailey PDI, were mixed.

For the current report we identified three new studies reported in five publications that assessed the effects of n-3 FA with or without other LCPUFA on neurodevelopmental outcomes. None of these studies could be pooled with studies in the original report.

DHA vs. Placebo

We identified two RCTs that assessed the effects of DHA supplementation alone on neurodevelopmental outcomes.

A 2004 RCT randomized 54 healthy term infants in Turkey within the first week of life to 4 months of Farleys First Milk (a DHA-supplemented infant formula [0.5% DHA]), or Nutrilon, a control formula.¹²² A group of 23 infants breastfed from birth served as a reference. At 4 months, brainstem maturation was assessed in the remaining 44 infants by measuring the decrease in brainstem auditory evoked potentials: All six measures (three absolute wave and three interpeak latencies) showed significantly greater maturation in the infants given the DHA-supplemented formula ($p=0.038-0.001$) and the breast fed infants ($P=0.04-0.001$), compared with the infants fed non-supplemented formula.

A 2011 RCT randomized 1,160 healthy term newborns in Italy to a daily supplement of oil containing DHA and vitamin D (0.4g/d DHA and 400IU, respectively) or vitamin D alone for 12 months to assess the effect on four measures of gross motor development.¹²³ At 12 months, among the remaining 1,091 infants, only one of the outcome measures, time to sitting without support, was achieved significantly faster in the DHA-supplemented infants. The remaining three outcome measures did not differ between intervention groups.

DHA plus AA vs. Placebo

The original report pooled the results of three RCTs ($n=184$) that assessed the effects of supplementing term infants with DHA plus AA on PDI scores at 12 months: the pooled weighted mean difference was -2.80 (95% CI -7.43, 1.82; I^2 36%), non-significantly favoring the control formula.

For the current report, we identified one RCT, reported in three publications, that assessed the effects of supplementing infant formula with DHA plus AA, but could not be pooled with the earlier studies. A 2003 multisite study conducted around Groningen in the Netherlands randomized 312 healthy term infants to one of two infant formulas: Nutricia Nutrilon formula supplemented with 0.30% DHA from egg yolk and tuna oil and 0.45% AA from egg yolk and

fungal oil or the same formula without DHA and AA. The fatty acid patterns of the fortified formula were similar to those of breast milk. A third group of 160 breastfed infants was also included. The intervention was continued for 2 months. Videographed general movements were analyzed at 3 months and quality was classified as described above.⁶⁶ The occurrence of mildly abnormal movements was significantly less frequent in the supplemented formula group than in the control group (adjusted OR 0.49[0.26, 0.92]p=0.032) and not significantly different from the breastfed group (p=0.87).

At 18 months' followup, toddlers were re-assessed with the PDI, the Hempel Test (to assess minor neurological dysfunction [MND]), and assessment of NOS (attrition was 5.5% and not selective).⁶⁵ In both univariate and multivariate analysis, the rate of MND, the NOS, and the PDI scores did not differ among the three groups (supplemented formula, control formula, and breast fed).

At 9 years of age, the children were re-assessed (attrition was 28% and boys with lower MDI scores were more heavily represented among the dropouts).⁶² The primary outcome was the NOS, based on the Touwen Neurological assessment of neurological dysfunction, and the MND. No differences were seen between the supplemented formula-fed group and the control group in the NOS or the ratios of neurologically normal, simple MND, and complex MND children. However, breastfed children were less likely to show fine manipulative dysfunction than either group of formula-fed children.

Table 13. RCTs for Neurological development

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Makrides et al., 2009¹¹³</p> <p>Study name: DINO</p> <p>Study dates: enrollment April 2001 to October 2005</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations</p> <p>Follow-up: 18 months {#4266}, {#4921}, {#4916}, {#8885}, {#9748}</p> <p>Follow-up article(s)^{111, 112, 100, 101, 114}</p>	<p>Study Population: Preterm infants Breast-feeding women</p> <p>Pregnant enrolled 545</p> <p>Infants enrolled 657</p> <p>Infants completers 614</p> <p>Lactating age: 30 years (5.5 years) NR</p> <p>Infant age: 4 days after birth (29 weeks gestation) 2 to 6 days after birth</p> <p>Race of Mother: White European (90%)</p>	<p>Inclusion Criteria: infants born at < 33 wk of gestation</p> <p>Exclusion Criteria: Infants born with major congenital or chromosomal abnormalities, lactating women for whom tuna oil was contraindicated(women with bleeding disorders or taking anticoagulants)</p>	<p>Start time: Infants 4 days after birth</p> <p>Duration: Infants until infants reached their "expected" date of delivery</p> <p>Arm 1: Placebo</p> <p>Description Soy oil capsules or regular preterm formula</p> <p>Manufacturer Clover Corporation</p> <p>Dose six 500-mg soy oil capsules</p> <p>Blinding all capsules were similar in size, shape, and color</p> <p>Maternal conditions</p> <p>Infant conditions</p> <p>Current smoker 25.1% during pregnancy</p> <p>Pre-term birth 100%</p> <p>Low birth weight 44.5%</p> <p>Other conditions 1 SGA 18.6%</p> <p>Arm 2: tuna oil capsules</p> <p>Description DHA-rich tuna oil capsules or high-DHA formula</p> <p>Manufacturer Clover Corporation</p> <p>N-3 Compositiondesigned to achieve a breast milk DHA concentration that was approximately 1% of total fatty acids without altering the naturally occurring concentration of arachidonic acid (AA) in breast milk</p> <p>Dose 6 500 mg capsules</p> <p>Maternal conditions</p> <p>Infant conditions</p> <p>DHA Capsules: Intended to achieve breast milk concentration of 1.0%.Formula: 1.0%</p> <p>AA Capsules: not intended to alter AA levels. Formula: 0.6%</p> <p>Current smoker 25.6% during pregnancy</p>	<p>Outcome psychomotor development index</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 335 mean 92.1 SD (16.3)</p> <p>Arm 2 Sample size 322 mean 93.1 SD (16.1)</p>
<p>Bouwstra et al., 2003⁶⁶</p> <p>Study name: Groningen LCPUFA study</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 472</p> <p>Infants completers 397</p>	<p>Inclusion Criteria: healthy term infants</p> <p>Exclusion Criteria: infants who had a</p>	<p>Start time: Infants Birth</p> <p>Duration: Infants 2 months</p> <p>Arm 1: Control formula</p>	<p>Outcome mildly abnormal general movements</p> <p>Follow-up time 3 months</p> <p>Arm 1 41/131 (31%)</p> <p>Arm 2 23/119 (19%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study dates: 1997-1999</p> <p>Study design: Trial randomized parallel</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 3 months ^{65, 62}</p> <p>Follow-up article(s) ^{61, 62, 63, 64, 65, 67, 68, 35}</p>	<p>Mother age: 31 (5) NR</p> <p>Infant age: Gestational age 39.6 wk (1.3) NR</p> <p>Race of Mother: White European (100)</p>	<p>congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.</p>	<p>Description Standard formula with no supplemental LCPUFA</p> <p>Brand name Nutrilon premium</p> <p>Manufacturer Zoetermeer, Netherlands</p> <p>Active ingredients linoleic acid (11mol%); ALA 1.27 mol%</p> <p>Dose ad lib</p> <p>Blinding not reported</p> <p>Maternal conditions</p> <p>Current smoker 32% during pregnancy</p> <p>Maternal abuse of alcohol/psychotropic drugs</p> <p>Alcohol USE during pregnancy 10%</p> <p>Arm 2: LCPUFA formula</p> <p>Description LCPUFA formula fortified with n-3s and n-6s</p> <p>Brand name NR</p> <p>Maternal conditions</p> <p>DHA 0.30% (by wt)</p> <p>AA h 0.45% (by wt)</p> <p>Current smoker 32% smoked during pregnancy</p> <p>Maternal abuse of alcohol/psychotropic drugs 13% used alcohol during pregnancy</p> <p>Arm 3: breastfed group</p> <p>Description breastfed, no formula, not randomized here - used as reference group</p> <p>Maternal conditions</p> <p>Current smoker 28% smoked during pregnancy</p> <p>Maternal abuse of alcohol/psychotropic drugs 38% consumed alcohol during pregnancy</p>	<p>Outcome normal-optimal general movements</p> <p>Follow-up time 3 months</p> <p>Arm 1 28/131 (21%)</p> <p>Arm 2 21/119 (18%)</p>
<p>Bouwstra et al., 2005⁶⁵</p> <p>Study name: Groningen LCPUFA study</p> <p>Study dates: 1997-2002</p> <p>Study design: Trial randomized parallel</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 472</p> <p>Infants completers 446</p> <p>Mother age: 31 years (5 years) NR</p> <p>Infant age: birth</p> <p>Race of Mother: White European (100%)</p>	<p>Inclusion Criteria: healthy term infants</p> <p>Exclusion Criteria: infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or</p>	<p>Start time: Infants Birth</p> <p>Duration: Infants 2 months</p> <p>Arm 1: Control group</p> <p>Description Standard formula</p> <p>Brand name Nutrilon premium</p> <p>Manufacturer Zoetermeer, Netherlands</p> <p>Active ingredients linoleic acid (11mol%); ALA 1.27 mol%</p> <p>Dose ad lib</p> <p>Maternal conditions</p> <p>Current smoker 31% during pregnancy</p> <p>Maternal abuse of alcohol/psychotropic drugs</p>	<p>Outcome Bayley PDI</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 169 mean 100.9 SD (13.6)</p> <p>Arm 2 Sample size 146 mean 99.4 SD (13.4)</p> <p>Outcome neurological optimality score</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 169 median 52 5, 95 percentile (42, 55)</p> <p>Arm 2 Sample size 146 median 52 5, 95 percentile (42, 55)</p> <p>Outcome number of children with minor neurological dysfunction</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Follow-up: 18 months ⁶⁶, ⁶²</p> <p>Follow-up article(s) ⁶¹, ⁶², ⁶³, ⁶⁴, ⁶⁶, ⁶⁷, ⁶⁸, ³⁵</p>		<p>disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.</p>	<p>Alcohol USE during pregnancy 8%</p> <p>Arm 2: LCPUFA formula</p> <p>Description LCPUFA formula</p> <p>Dose ad lib</p> <p>Maternal conditions</p> <p>DHA 0.30% DHA</p> <p>AA 0.45% AA</p> <p>Current smoker 31% during pregnancy</p> <p>Maternal abuse of alcohol/psychotropic drugs 9%</p> <p>used alcohol during pregnancy</p> <p>Arm 3: breast feeding group</p> <p>Description breast fed, no formula</p> <p>Maternal conditions</p> <p>Current smoker 19% smoked during pregnancy</p> <p>Maternal abuse of alcohol/psychotropic drugs 24%</p> <p>used alcohol during pregnancy</p>	<p>Follow-up time 18 months</p> <p>Arm 1 8/169 (5%)</p> <p>Arm 2 10/146 (7%)</p>
<p>Goor et al., 2011⁶⁴</p> <p>Study name: Groningen LCPUFA study</p> <p>Study dates: 2004-2009</p> <p>Study design: Trial randomized parallel</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 18 months (multiple IDs)</p> <p>Follow-up article(s) ⁶¹, ⁶², ⁶³, ⁶⁵, ⁶⁶, ⁶⁷, ⁶⁸, ³⁵</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 119</p> <p>Infants enrolled 119</p> <p>Infants completers 114</p> <p>Pregnant age: Placebo: 32.7 DHA: 32.5 DHA+AA: 32.9 (Placebo: 5.1 DHA: 4.4 DHA+AA: 4.8)</p> <p>Infant age: 18 months</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: women with a first or second low-risk singleton pregnancy, between the 14th and 20th weeks of pregnancy</p> <p>Exclusion Criteria: women with vegetarian or vegan diets; women with diabetes mellitus; birth complications</p>	<p>Start time: Pregnant 14th-20th week pregnancy Lactating 3 months after delivery Mothers 3 months after delivery Infants NR</p> <p>Duration: Pregnant NR Lactating 33-39 weeks Mothers 33-39 weeks Infants NR</p> <p>Arm 1: placebo</p> <p>Description Soy bean oil</p> <p>Brand name none</p> <p>Arm 2: DHA</p> <p>Description DHA plus soy bean oil</p> <p>Brand name Marinol D40</p> <p>Manufacturer Lipid Nutrition B.V., Wormerveer, The Netherlands; AA:</p> <p>Dose 1 capsule DHA and 1 capsule soy bean oil once a day</p> <p>ALA 32 mg/d</p> <p>DHA 220 mg/d</p> <p>EPA 34 mg/d</p> <p>Arm 3: DHA+AA</p> <p>Description DHA plus AA</p> <p>Brand name AA: no brand name</p> <p>Manufacturer Wuhan Alking Bioengineering Co. Ltd., Wuhan, China</p> <p>Dose 2 capsules once a day</p> <p>ALA 7 mg/d</p>	<p>Outcome fluency score</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 34 median 10 range (6-12)</p> <p>Arm 2 Sample size 41 median 9 range (5-12)</p> <p>Arm 3 Sample size 39 median 10 range (4-12)</p> <p>Outcome neurological optimality score</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 34 median 47.5 range (29-55)</p> <p>Arm 2 Sample size 41 median 46 range (30-56)</p> <p>Arm 3 Sample size 39 median 48 range (25-57)</p> <p>Outcome prevalence of complex minor neurological dysfunction</p> <p>Follow-up time 18 months</p> <p>Arm 1 5/34 (14.7%)</p> <p>Arm 2 3/41 (7.3%)</p> <p>Arm 3 5/39 (12.8%)</p> <p>Outcome prevalence of normal neurological condition</p> <p>Follow-up time 18 months</p> <p>Arm 1 20/34 (58.8%)</p> <p>Arm 2 24/41 (58.5%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			DHA 220 mg/d EPA 36 mg/d AA 220 mg per capsule	Arm 3 28/39 (71.8%) Outcome prevalence of simple minor neurological dysfunction Follow-up time 18 months Arm 1 9/34 (26.5%) Arm 2 14/41 (34.1%) Arm 3 6/39 (15.4%) Outcome psychomotor development index Follow-up time 18 months Arm 1 Sample size 34 mean 91.7 SD (8.3) Arm 2 Sample size 41 mean 95.8 SD (11.4) Arm 3 Sample size 39 mean 92.4 SD (8.8)
de Jong et al., 2010 ⁶² Study name: Groningen LCPUFA study Study dates: 1997-2008 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Government Follow-up: 9 years 6267 and 6265 Follow-up article(s) ^{61, 63, 64, 65, 66, 67, 68, 35}	Study Population: Healthy infants Infants enrolled 474 Infants completers 341 Infant age: Gestational age 39.6 wk (1.3 weeks) NR Race of Mother: White European (100)	Inclusion Criteria: healthy term infants Exclusion Criteria: Infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.	Start time: Infants birth Duration: NR Arm 1: control group Description standard formula Manufacturer Zoetermeer, Netherlands Active ingredients linoleic acid (11mol%); ALA 1.27 mol% Blinding NR Arm 2: Omega 3 group Description LCPUFA formula Brand name Nutrilon Premium Manufacturer Nutricia, Zoetermeer, The Netherlands Dose NR DHA 0.30 % (by weight) AA 0.45 % (by weight) Arm 3: Breast fed group Description Breast feeding only - no formula	Outcome Touwen examination: neurologically normal Follow-up time 9 years Arm 1 56/123 (46%) Arm 2 44/91 (48%)
van Goor et al., 2010 ³⁵ Study name: Groningen LCPUFA study Study dates: enrollment from December 2004 until December 2006	Study Population: Healthy pregnant women Breast-feeding women Pregnant enrolled 183 Pregnant completers 125 Infants completers 119	Inclusion Criteria: healthy women with a first or second low-risk singleton pregnancy Exclusion Criteria: women with vegetarian or vegan diets and women with diabetes	Start time: Pregnant 14 to 20 weeks gestation Infants 14 to 20 weeks gestation Duration: Pregnant until 3 months after delivery Infants until 3 months of age Arm 1: placebo Description soybean oil capsule Manufacturer Wuhan Alking Bioengineering	Outcome general movements: number definitely abnormal Follow-up time 12 weeks Arm 1 0/36 (0%) Arm 2 1/42 (2.38%) Arm 3 0/41 (0%) Follow-up time 2 weeks Arm 1 1/36 (2.78%) Arm 2 0/42 (0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study design: Trial randomized parallel</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: 12 weeks ⁶⁰</p> <p>Follow-up article(s) ^{61, 62, 63, 64, 65, 66, 67, 68}</p>	<p>Pregnant age: 32 years (5 years)</p> <p>Infant age: 14 to 20 weeks gestation</p> <p>Race of Mother: NR (100)</p>	<p>mellitus</p>	<p>Active ingredients standard dose vitamins and minerals</p> <p>N-3 Composition.</p> <p>Dose 2 capsules</p> <p>Maternal conditions</p> <p>ALA 60 mg</p> <p>DHA 0</p> <p>EPA 0</p> <p>AA 0</p> <p>Other dose 1 LA 535 mg</p> <p>Current smoker 2%</p> <p>Arm 2: DHA group</p> <p>Description DHA fish oil capsule</p> <p>Manufacturer Wuhan Alking Bioengineering</p> <p>Active ingredients standard dose vitamins and minerals</p> <p>Dose 2 capsules</p> <p>Maternal conditions</p> <p>ALA 32 mg</p> <p>DHA 220 mg</p> <p>EPA 34 mg</p> <p>AA 15 mg</p> <p>Current smoker 2%</p> <p>Other comment 2 LA 274 mg</p> <p>Arm 3: DHA + AA group</p> <p>Description DHA + AA capsule</p> <p>Brand name Marinol D40</p> <p>Manufacturer Lipid Nutrition B.V., Wormerveer, The Netherlands</p> <p>Active ingredients standard dose vitamins and minerals</p> <p>Dose 2 capsules</p> <p>Maternal conditions</p> <p>ALA 7 mg</p> <p>DHA 220 mg</p> <p>EPA 36 mg</p> <p>AA 220 mg</p> <p>Other dose 2 LA 46 mg</p> <p>Current smoker 3%</p>	<p>Arm 3 0/41 (0%)</p> <p>Outcome general movements: number mildly abnormal</p> <p>Follow-up time 12 weeks</p> <p>Arm 1 11/36 (30.56%)</p> <p>Arm 2 25/42 (59.52%)</p> <p>Arm 3 14/41 (34.15%)</p> <p>Follow-up time 2 weeks</p> <p>Arm 1 11/36 (30.56%)</p> <p>Arm 2 20/42 (47.62%)</p> <p>Arm 3 15/41 (36.59%)</p> <p>Outcome general movements: number normal optimal</p> <p>Follow-up time 12 weeks</p> <p>Arm 1 2/36 (5.56%)</p> <p>Arm 2 0/42 (0%)</p> <p>Arm 3 1/41 (2.44%)</p> <p>Follow-up time 2 weeks</p> <p>Arm 1 1/36 (2.78%)</p> <p>Arm 2 0/42 (0%)</p> <p>Arm 3 1/41 (2.44%)</p> <p>Outcome general movements: number normal suboptimal</p> <p>Follow-up time 12 weeks</p> <p>Arm 1 23/36 (63.89%)</p> <p>Arm 2 16/42 (38.1%)</p> <p>Arm 3 26/41 (63.41%)</p> <p>Follow-up time 2 weeks</p> <p>Arm 1 19/36 (52.78%)</p> <p>Arm 2 17/42 (40.48%)</p> <p>Arm 3 22/41 (53.66%)</p> <p>Outcome neonatal neurological classification: number definitely abnormal</p> <p>Follow-up time 2 weeks</p> <p>Arm 1 0/36 (0%)</p> <p>Arm 2 0/42 (0%)</p> <p>Arm 3 0/41 (0%)</p> <p>Outcome neonatal neurological classification: number mildly abnormal</p> <p>Follow-up time 2 weeks</p> <p>Arm 1 7/36 (19.44%)</p> <p>Arm 2 6/42 (14.29%)</p> <p>Arm 3 8/41 (19.51%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Outcome neonatal neurological classification: number normal Follow-up time 2 weeks Arm 1 28/36 (77.78%) Arm 2 35/42 (83.33%) Arm 3 33/41 (80.49%)
<p>Meldrum et al., 2012¹²⁴</p> <p>Study name: Infant FishOil Supplementation Study (IFOS)</p> <p>Study dates: recruitment from June 2005 through October 2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, None, Manufacturer supplied product</p> <p>Follow-up article(s) Protocol ID 5460},¹²⁵</p>	<p>Study Population: Pregnant women with allergies</p> <p>Pregnant enrolled 420</p> <p>Infants enrolled 420 Infants completers 287</p> <p>Mother age: NR (NR) NR</p> <p>Infant age: Birth (NA) NA</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: allergic pregnant women were recruited as their infants are at a higher risk of developing allergic disease. Maternal atopy was defined by at least one positive skin prick test to at least one of a defined panel of allergens.</p> <p>Exclusion Criteria: maternal smoking, a pre-existing medical condition or high-risk pregnancy, more than three fish meals consumed per week or fish oil intake during pregnancy in excess of 1000 mg/d, preterm delivery, and infants with significant congenital abnormalities or medical conditions.</p>	<p>Start time: Infants birth</p> <p>Duration: Infants 6 months</p> <p>Arm 1: placebo Description olive oil capsule Manufacturer Ocean Nutrition, Canada Active ingredients 66.6 % n-9 oleic acid Viability he composition was regularly tested by an independent laboratory during the trial Dose one 650 mg capsule Blinding image and scent matched Arm 2: fish oil capsul Manufacturer Ocean Nutrition, Canada Viability he composition was regularly tested by an independent laboratory during the trial. Dose one 650 mg capsule DHA 280 mg EPA 110 mg</p>	<p>Outcome Categorical Child Behavior Checklist: Sleep problems - number with t-score>59</p> <p>Follow-up time 18 months</p> <p>Arm 1 56/144 (39%) Arm 2 54/125 (43.5%)</p>
<p>Agostoni et al., 2009¹²³</p> <p>Study name: NR</p> <p>Study dates: Enrollment occurred May and June 2005; 1-year followup</p> <p>Study design: Trial randomized parallel</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 1160 Infants withdrawals 69 Infants completers 1091</p> <p>Mother age: 32 years (4.5 years) NR</p>	<p>Inclusion Criteria: weight at birth 2500 g or more, gestational age between 37 and 42 completed weeks, single birth, absence of neonatal or birth abnormalities, Apgar score 7 or higher at 5 min, and white parents.</p>	<p>Start time: Infants 1 day after discharge from birth hospital</p> <p>Duration: Infants 1 year</p> <p>Arm 1: placebo Description oral liquid Manufacturer Humana Italia SpA Active ingredients 400 IU vitamin D3 Viability Parents were advised to store the bottles in</p>	<p>Outcome age achieving gross motor: hands-and-knees crawling</p> <p>Follow-up time varies</p> <p>Arm 1 Sample size 476 mean 39.4 SD (6.2) Arm 2 Sample size 482 mean 38.9 SD (6.4)</p> <p>Outcome age achieving gross motor: sitting without support</p> <p>Follow-up time varies</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Location: Italy</p> <p>Funding source / conflict: Manufacturer supplied product</p>	<p>Infant age: intervention began 1 day after discharge (NA) NA</p> <p>Race of Mother: White European (100%)</p>	<p>Exclusion Criteria: presence of neonatal diseases requiring hospitalization for 7 days or more; involvement of neonate in another clinical study; unknown father; and parents unable to understand the protocol requirements, to fill out the infant's diary, or to understand and speak the Italian language adequately.</p>	<p>a dry and fresh environment.</p> <p>N-3 Composition.</p> <p>Dose 1 mL once per day</p> <p>Blinding Intervention and placebo preparations were identical in aroma, taste, and texture</p> <p>Total N-3 0</p> <p>Arm 2: Human Italia SpA</p> <p>Active ingredients 400 IU vitamin D3</p> <p>Viability Parents were advised to store the bottles in a dry and fresh environment.</p> <p>Dose 1 mL once per day</p> <p>DHA 20 mg DHA/ml</p>	<p>Arm 1 Sample size 542 mean 28.3 SD (4.2)</p> <p>Arm 2 Sample size 551 mean 26.8 SD (4.2)</p> <p>Outcome age achieving gross motor: standing alone</p> <p>Follow-up time varies</p> <p>Arm 1 Sample size 542 mean 50.1 SD (8.1)</p> <p>Arm 2 Sample size 549 mean 49.2 SD (7.6)</p> <p>Outcome age achieving gross motor: walking alone</p> <p>Follow-up time varies</p> <p>Arm 1 Sample size 542 mean 55.8 SD (6.7)</p> <p>Arm 2 Sample size 549 mean 54.9 SD (6.8)</p>
<p>Clandinin et al., 2005¹⁰⁴</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Trial randomized parallel</p> <p>Location: Canada</p> <p>Funding source / conflict: Industry</p>	<p>Study Population: Preterm infants</p> <p>Infants enrolled 361 preterm+105 term breastfed Infants completers 179 preterm and 76/105 term breastfed</p> <p>Infant age: 30.6 weeks postmenstrual age 24-36 weeks postmenstrual age</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Phase I: gestational age <35 weeks PMA and received <10 total days of enteral feedings of >30 mL/kg per day. Infants initially fed human milk were not enrolled unless formula was started within 10 days after completing the first day of human milk feeding Phase II: completion of phase I and >=80% enteral intake from study formula during hospitalization and 100% of caloric intake from study formula at completion of phase 1. Birth weight<1500g</p> <p>Exclusion Criteria: congenital abnormalities of the gastrointestinal</p>	<p>Start time: Infants 10 days of age</p> <p>Duration: Infants 118 weeks</p> <p>Arm 1: Control</p> <p>Description Non-supplemented premature, discharge, and term formula</p> <p>Dose Ad lib</p> <p>Blinding Not reported</p> <p>Infant conditions</p> <p>Pre-term birth 119 (100%)</p> <p>Arm 2: Algal-DHA</p> <p>Description supplemented premature infant formula supplemented with DHA from algal oil</p> <p>Manufacturer Martek Biosciences</p> <p>Dose ad lib</p> <p>DHA 17mg/100kcal (0.33% by weight)</p> <p>EPA 0.1% by weight</p> <p>AA 34mg/100kcal (0.67% by weight)</p> <p>Arm 3: Fish-DHA</p> <p>Description Premature infant formula supplemented with DHA from tuna fish oil</p> <p>Manufacturer Martek Biosciences</p> <p>Dose ad lib</p> <p>DHA 17mg DHA/100 kcal</p>	<p>Outcome BSID II PDI</p> <p>Follow-up time 118 weeks</p> <p>Arm 1 Sample size 54 mean 83 SE (2)</p> <p>Arm 2 Sample size 46 mean 88 SE (2)</p> <p>Arm 3 Sample size 59 mean 88 SE (2)</p> <p>Arm 4 Sample size 59 mean 98 SE (2)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		tract, hepatitis, hepatic or biliary pathology, necrotizing enterocolitis confirmed before enrollment, or history of underlying disease or congenital malformation likely to interfere with evaluation	AA 34mg/100 kcal Arm 4: Reference Description Breast fed term infants	
<p>Fang et al., 2005¹²⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Trial randomized parallel</p> <p>Location: Taiwan</p> <p>Funding source / conflict: Manufacturer supplied product</p>	<p>Study Population: Preterm infants</p> <p>Infants enrolled 28 Infants withdrawals 1 Infants completers 27</p> <p>Infant age: 1 week (mean gestation age 33 weeks) (0.5 week) NA</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: (1) A gestational age at birth between 30 and 37 weeks; (2) Normal fundus oculi; (3) Recruitment prior to commencement of feeding</p> <p>Exclusion Criteria: (1) Breast feeding; (2) A maternal history of infection, diabetes mellitus, gestational diabetes mellitus, cocaine or alcohol abuse, systemic diseases or if intrauterine growth retardation had been diagnosed during pregnancy; (3) Major congenital abnormality; (4) Severe intraventricular hemorrhage > grade 2; (5) Cystic periventricular leukomalacia; (6) Retinopathy of prematurity stage 2; (7) Bronchopulmonary dysplasia on radiographs or oxygen usage 28 days; (8) Body weight less than the third</p>	<p>Start time: Infants 1 week after birth</p> <p>Duration: Infants 24 weeks</p> <p>Arm 1: placebo Description infant formula based on the composition of human milk Brand name Neoangelac Manufacturer Multipower Enterprise Corporation N-3 Composition. Dose Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months N-6 N-3 10:1 linoleic:linolenic Arm 2: Neoangelac Plus Description Neoangelac supplemented with Omega 3 Brand name Neoangelac Plus Manufacturer Multipower Enterprise Corporation Dose Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months DHA 0.05% AA 0.10%</p>	<p>Outcome psychomotor development index Follow-up time 12 months Arm 1 Sample size 11 mean 86.7 SD (11.1) Arm 2 Sample size 16 mean 98 SD (5.8) Follow-up time 6 months Arm 1 Sample size 11 mean 95.4 SD (13.2) Arm 2 Sample size 16 mean 102.2 SD (10.5)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		percentile; (9) Surgical intervention for necrotizing enterocolitis (10) Mechanical ventilation after achieving enteral intake > 110 kcal/kg per day; (11) A 5-min Apgar score < 7; (12) Administration of blood transfusion, blood products, or parenteral lipids with DHA or AA.		
<p>Judge et al., 2012³⁹</p> <p>Study name: NR</p> <p>Study dates: nr</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: NR</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 48</p> <p>Pregnant age: Treatment group: 23.93 Placebo: 23.86 (Treatment group: 4.32 Placebo: 4.53)</p> <p>Race of Mother: White European (Treatment: 11.1%, Placebo: 0%) Black (Treatment: 18.5%, Placebo: 4.8%) Asian (Treatment: 3.7%, Placebo: 0%) Hispanic (Treatment: 59.3%, Placebo: 80.9%) NR (Treatment: 7.4%, 3 (14.3%))</p>	<p>Inclusion Criteria: The women were either primiparous or had not been pregnant for the past 2 years.</p> <p>Exclusion Criteria: parity greater than 5, history of chronic hypertension, hyperlipidemia, renal, liver or heart disease, thyroid disorder, multiple gestations or pregnancy induced complications including hypertension, preeclampsia or preterm labor, smoking and psychiatric disorders. Women who were treated during labor with analgesics such as Stadol (butorphanol tartrate), that may cause infant respiratory distress were also excluded. In addition, infants born preterm and infants with less than 4 h of crib time in the first and second days postpartum were</p>	<p>Start time: Pregnant 24 weeks gestation</p> <p>Duration: Pregnant until delivery</p> <p>Arm 1: Placebo Description Control group Manufacturer estec, S.A., Switzerland Blinding The total macronutrient content was the same in both the DHA and placebo bars with respect to carbohydrate, protein and fat, however, the DHA bars contained fish oil (300 mg DHA) and the placebo bars contained corn oil.</p> <p>Arm 2: DHA Description Intervention group Manufacturer estec, S.A., Switzerland Dose average of 5 bars weekly DHA 300 mg EPA-DHA 8:1 ratio of DHA to EPA</p>	<p>Outcome Infant sleep: Active Sleep (AS, %)</p> <p>Follow-up time 1 day after birth</p> <p>Arm 1 Sample size 19 mean 51.81 SD (10.43)</p> <p>Arm 2 Sample size 27 mean 49.39 SD (10.32)</p> <p>Follow-up time 2 days after birth</p> <p>Arm 1 Sample size 15 mean 51.7 SD (11.13)</p> <p>Arm 2 Sample size 24 mean 51.57 SD (14.54)</p> <p>Outcome Infant sleep: Active–Quiet Sleep Transition (AQST, %)</p> <p>Follow-up time 1 day after birth</p> <p>Arm 1 Sample size 19 mean 0.53 SD (0.23)</p> <p>Arm 2 Sample size 27 mean 0.59 SD (0.37)</p> <p>Follow-up time 2 days after birth</p> <p>Arm 1 Sample size 15 mean 0.41 SD (0.27)</p> <p>Arm 2 Sample size 24 mean 0.47 SD (0.3)</p> <p>Outcome Infant sleep: Arousals in AS (Ar/AS)</p> <p>Follow-up time 1 day after birth</p> <p>Arm 1 Sample size 19 mean 20.41 SD (4.39)</p> <p>Arm 2 Sample size 27 mean 17.41 SD (4.71)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		excluded from the analyses.		<p>Follow-up time 2 days after birth</p> <p>Arm 1 Sample size 15 mean 24.67 SD (6.82)</p> <p>Arm 2 Sample size 24 mean 24.04 SD (7.04)</p> <p>Outcome Infant sleep: Arousals in QS (Ar/QS)</p> <p>Follow-up time 1 day after birth</p> <p>Arm 1 Sample size 19 mean 5.89 SD (6.01)</p> <p>Arm 2 Sample size 27 mean 2.7 SD (2.65)</p> <p>Follow-up time 2 days after birth</p> <p>Arm 1 Sample size 15 mean 5.44 SD (4.07)</p> <p>Arm 2 Sample size 24 mean 3.55 SD (3.98)</p> <p>Outcome Infant sleep: Mean Sleep Period (LSP, min)</p> <p>Follow-up time 1 day after birth</p> <p>Arm 1 Sample size 19 mean 185.95 SD (79.75)</p> <p>Arm 2 Sample size 27 mean 228.19 SD (104.89)</p> <p>Follow-up time 2 days after birth</p> <p>Arm 1 Sample size 15 mean 202.6 SD (123.18)</p> <p>Arm 2 Sample size 24 mean 190.75 SD (102.75)</p> <p>Outcome Infant sleep: Mean Sleep Period (MSP, min)</p> <p>Follow-up time 1 day after birth</p> <p>Arm 1 Sample size 19 mean 46.09 SD (17.6)</p> <p>Arm 2 Sample size 27 mean 48.03 SD (17.55)</p> <p>Follow-up time 2 days after birth</p> <p>Arm 1 Sample size 15 mean 48.85 SD (29.99)</p> <p>Arm 2 Sample size 24 mean 48.67 SD (21.18)</p> <p>Outcome Infant sleep: Wakefulness (W, %)</p> <p>Follow-up time 1 day after birth</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				<p>Arm 1 Sample size 19 mean 27.59 SD (11.54)</p> <p>Arm 2 Sample size 27 mean 29.57 SD (13.56)</p> <p>Follow-up time 2 days after birth</p> <p>Arm 1 Sample size 15 mean 28.95 SD (12.14)</p> <p>Arm 2 Sample size 24 mean 30.71 SD (18.92)</p> <p>Outcome Infant sleep: quiet sleep (QS,%)</p> <p>Follow-up time 1 day after birth</p> <p>Arm 1 Sample size 19 mean 15.14 SD (4.26)</p> <p>Arm 2 Sample size 27 mean 15.88 SD (5.1)</p> <p>Follow-up time 2 days after birth</p> <p>Arm 1 Sample size 15 mean 13.7 SD (4.76)</p> <p>Arm 2 Sample size 24 mean 12.7 SD (5.85)</p> <p>Outcome Infant sleep: Active sleep bout length (ASBL, min)</p> <p>Follow-up time 1 day after birth</p> <p>Arm 1 Sample size 19 mean 28.93 SD (9.67)</p> <p>Arm 2 Sample size 27 mean 29 SD (7.07)</p> <p>Follow-up time 2 days after birth</p> <p>Arm 1 Sample size 15 mean 29.81 SD (12.5)</p> <p>Arm 2 Sample size 24 mean 30.48 SD (9.14)</p> <p>Outcome Infant sleep: Active/Quiet Sleep Ratio(AS:QS)</p> <p>Follow-up time 1 day after birth</p> <p>Arm 1 Sample size 19 mean 3.83 SD (2.15)</p> <p>Arm 2 Sample size 27 mean 3.38 SD (1.1)</p> <p>Follow-up time 2 days after birth</p> <p>Arm 1 Sample size 15 mean 4.56 SD (3.13)</p> <p>Arm 2 Sample size 24 mean 4.46 SD (2.14)</p> <p>Outcome Infant sleep: Quiet sleep bout</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				length (QSBL, min) Follow-up time 1 day after birth Arm 1 Sample size 19 mean 21.81 SD (4.93) Arm 2 Sample size 27 mean 22.74 SD (5.73) Follow-up time 2 days after birth Arm 1 Sample size 15 mean 20.59 SD (4.98) Arm 2 Sample size 24 mean 18.75 SD (6.86) Outcome Infant sleep: Sleep–Wake Transition (T, %) Follow-up time 1 day after birth Arm 1 Sample size 19 mean 4.92 SD (1.48) Arm 2 Sample size 27 mean 4.57 SD (1.33) Follow-up time 2 days after birth Arm 1 Sample size 15 mean 5.23 SD (1.88) Arm 2 Sample size 24 mean 4.5 SD (1.39) Outcome Infant sleep: Sleep–Wake Transition (T, %) Follow-up time 1 day after birth Arm 1 Sample size 19 mean 4.92 SD (1.48) Arm 2 Sample size 27 mean 4.57 SD (1.33) Follow-up time 2 days after birth Arm 1 Sample size 15 mean 5.23 SD (1.88) Arm 2 Sample size 24 mean 4.5 SD (1.39)
Tofail et al., 2006 ⁸¹ Study name: NR Study dates: enrollment January to March 2000 Study design: Trial randomized parallel	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 400 Pregnant completers 151 Pregnant age: 22.7 years (4.35 years) NR	Inclusion Criteria: seems as if all pregnant women at 25 weeks gestation were enrolled, no inclusion criteria specified Exclusion Criteria: NR	Start time: Pregnant 25 weeks gestation Duration: Pregnant until birth Arm 1: placebo Description soy oil capsule N-3 Composition. Dose 4 one gram capsules per day Blinding capsules were identical in appearance Other dose 1 LNA 0.27 g	Outcome psychomotor development index Follow-up time 10 months Arm 1 Sample size 124 mean 100.5 SD (10.1) Arm 2 Sample size 125 mean 101.7 SD (10.9)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: Bangladesh Funding source / conflict: Government Follow-up: 10 months	Race of Mother: Asian (100%)		Other dose 2 linoleic acid 2.25 g Arm 2: DHA supplement Description fish oil capsules Dose 4 one gram capsules per day DHA 1.2 g EPA 1.8 g	
Unay et al., 2004 ¹²² Study name: NR Study dates: 2000-2001 Study design: Trial randomized parallel Location: Turkey Funding source / conflict: NR	Study Population: Healthy infants Infants enrolled 54 Infants completers 44 Infant age: NR (term) Race of Mother: NR (NR)	Inclusion Criteria: healthy, full term newborns of appropriate size for gestational age, who were not going to be breast fed because that was the mother's wish or because of maternal illness or medication incompatible with breast feeding just after birth Exclusion Criteria: Perinatal asphyxia, central nervous system infection, congenital malformation, or significant hyperbilirubinaemia	Start time: Infants week 1 Duration: Infants 16 weeks Arm 1: Formula B Description Infant formula without added DHA Brand name Nutrilon I Manufacturer NV Nutricia Netherlands Active ingredients Linoleic acid 11.2gm/100gm fat N-3 Composition. ALA 2.2g/100g fat AA Trace Arm 2: Formula A Description DHA-containing formula Brand name Farley's First Milk Manufacturer HJ Heinz UK Blinding not reported ALA 1.2g/100gm DHA 0.5g/100gm AA Trace Arm 3: Human milk Description Breast milk Active ingredients Linoleic acid: 10.85 gm/100gm fat ALA 1.03gm/100g fat DHA 0.25 gm/100gm fat AA 0.46 gm/100g fat	Outcome brainstem auditory evoked potentials: interpeak latency I-III Follow-up time 16 weeks Arm 1 Sample size 22 mean decrease 0.25 SD (0.14) Arm 2 Sample size 22 mean decrease 0.34 SD (0.16) Outcome brainstem auditory evoked potentials: interpeak latency I-V Follow-up time 16 weeks Arm 1 Sample size 22 mean decrease 0.33 SD (0.16) Arm 2 Sample size 22 mean decrease 0.47 SD (0.2) Outcome brainstem auditory evoked potentials: interpeak latency III-V Follow-up time 16 weeks Arm 1 Sample size 22 mean decrease 0.08 SD (0.07) Arm 2 Sample size 22 mean decrease 0.14 SD (0.1) Outcome brainstem auditory evoked potentials: wave I Follow-up time 16 weeks Arm 1 Sample size 22 mean decrease 0.27 SD (0.14) Arm 2 Sample size 22 mean decrease 0.35 SD (0.13) Outcome brainstem auditory evoked potentials: wave III Follow-up time 16 weeks Arm 1 Sample size 22 mean decrease 0.52 SD (0.15) Arm 2 Sample size 22 mean decrease 0.69 SD (0.16) Outcome brainstem auditory evoked potentials: wave V

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time 16 weeks Arm 1 Sample size 22 mean decrease 0.6 SD (0.11) Arm 2 Sample size 22 mean decrease 0.83 SD (0.18)
<p>Stein et al., 2012³²</p> <p>Study name: POSGRAD</p> <p>Study dates: Feb 2005-Feb 2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: NR</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 3364</p> <p>Follow-up article(s) ^{31, 72}</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 1094 Pregnant withdrawals 63 Pregnant completers 900</p> <p>Pregnant age: 26.3 (4.6-4.8)</p> <p>Infant age: 39.1 (1.7-1.8)</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: Singleton live births without congenital anomalies</p> <p>Exclusion Criteria: 3364: high risk pregnancy, (history and prevalence of pregnancy complications, including abruptio placentae, preeclampsia, pregnancy-induced hypertension, any serious bleeding episode in the current pregnancy, and physician referral); lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplement, or chronic use of certain medication(eg. epilepsy medications)</p>	<p>Start time: Pregnant 18-22 wk</p> <p>Duration: Pregnant to birth</p> <p>Arm 1: Placebo Description A mixture of cod and soy oil Manufacturer Martek Biosciences Blinding "Participants and members of the study team were unaware of the treatment scheme throughout the intervention period of the study"</p> <p>Arm 2: DHA Description DHA 400 mg/d Manufacturer Martek Biosciences Dose 2 capsule per day DHA 2*200mg</p>	<p>Outcome auditory evoked responses: latency 1 Follow-up time 1 month Arm 1 Sample size 377 mean 1.63 SD (0.14) Arm 2 Sample size 372 mean 1.62 SD (0.16) Follow-up time 3 months Arm 1 Sample size 334 mean 1.58 SD (0.15) Arm 2 Sample size 330 mean 1.58 SD (0.15) Outcome auditory evoked responses: latency 1-3 Follow-up time 1 month Arm 1 Sample size 377 mean 2.57 SD (0.36) Arm 2 Sample size 372 mean 2.56 SD (0.27) Follow-up time 3 months Arm 1 Sample size 334 mean 2.44 SD (0.28) Arm 2 Sample size 330 mean 2.45 SD (0.28) Outcome auditory evoked responses: latency 1-5 Follow-up time 1 month Arm 1 Sample size 377 mean 4.93 SD (0.36) Arm 2 Sample size 372 mean 4.91 SD (0.39) Follow-up time 3 months Arm 1 Sample size 334 mean 4.75 SD (0.39) Arm 2 Sample size 330 mean 4.72 SD (0.39) Outcome auditory evoked responses: latency 3</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				<p>Follow-up time 1 month</p> <p>Arm 1 Sample size 377 mean 4.19 SD (0.33)</p> <p>Arm 2 Sample size 372 mean 4.18 SD (0.32)</p> <p>Follow-up time 3 months</p> <p>Arm 1 Sample size 334 mean 4.02 SD (0.32)</p> <p>Arm 2 Sample size 330 mean 4.03 SD (0.33)</p> <p>Outcome auditory evoked responses: latency 3-5</p> <p>Follow-up time 1 month</p> <p>Arm 1 Sample size 377 mean 2.37 SD (0.3)</p> <p>Arm 2 Sample size 372 mean 2.37 SD (0.34)</p> <p>Follow-up time 3 months</p> <p>Arm 1 Sample size 334 mean 2.31 SD (0.35)</p> <p>Arm 2 Sample size 330 mean 2.28 SD (0.33)</p> <p>Outcome auditory evoked responses: latency 5</p> <p>Follow-up time 1 month</p> <p>Arm 1 Sample size 377 mean 6.55 SD (0.42)</p> <p>Arm 2 Sample size 372 mean 6.52 SD (0.48)</p> <p>Follow-up time 3 months</p> <p>Arm 1 Sample size 334 mean 6.33 SD (0.4)</p> <p>Arm 2 Sample size 330 mean 6.29 SD (0.42)</p>
<p>Jensen et al., 2005¹²¹</p> <p>Study name: Unnamed Trial B</p> <p>Study dates: <2004</p> <p>Study design: Trial randomized parallel</p>	<p>Study Population: Breast-feeding women</p> <p>Lactating enrolled 227 Lactating completers 174</p> <p>Infants enrolled 230 Infants completers 177</p>	<p>Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age ≥ 37 wk, infant birth weight between 2500 and 4200 g</p> <p>Exclusion Criteria:</p>	<p>Start time: Lactating 5 days after delivery Infants 5 days after birth</p> <p>Duration: Lactating 4 months Infants 4 months</p> <p>Arm 1: placebo</p> <p>Description capsule containing corn & soy oil Manufacturer Martek Biosciences</p> <p>Purity Data 15% saturated fatty acids, 23.5%</p>	<p>Outcome Bayley PDI</p> <p>Follow-up time 30 months</p> <p>Arm 1 Sample size 65 mean 108.4 SD (13.8)</p> <p>Arm 2 Sample size 68 mean 116.8 SD (15.2)</p> <p>Outcome Clinical Linguistic and Auditory Milestone Scale (CLAMS)</p> <p>Follow-up time 30 months</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Location: US</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up article(s) ¹²⁰</p>	<p>Lactating enrolled 227 Lactating completers 174</p> <p>Lactating age: 31.5 years (5 years) 18-40</p> <p>Infant age: birth (NA) NA</p> <p>Race of Mother: NR</p>	<p>chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant</p>	<p>monounsaturated fatty acids, 56.3% linoleic acid (18: 2n_x0001_6), and 3.9% _x0001_-linolenic acid (18:3n_x0001_3)</p> <p>N-3 Composition.</p> <p>Dose 1 capsule</p> <p>Blinding identical capsules</p> <p>ALA 56.3% linoleic acid (18: 2n_x0001_6), 3.9% _x0001_-linolenic acid (18:3n_x0001_3)</p> <p>Total N-3 57.2%</p> <p>Arm 2: DHA algal triacylglycerol (DHASCO)</p> <p>Description DHA capsule</p> <p>Brand name DHASCO</p> <p>Manufacturer Martek Biosciences</p> <p>Purity Data 44%saturatedfattyacids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n_x0001_6), and 41.7% DHA (22:6n-3) by weight</p> <p>N-3 Composition 0.8% linoleic acid (18:2n_x0001_6), 41.7% DHA (22:6n_x0001_3)</p> <p>Dose 1 capsule</p> <p>ALA 0.8%</p> <p>DHA 200 mg</p> <p>Total N-3 42.5%</p>	<p>Arm 1 Sample size 72 mean 106.6 SD (14.9)</p> <p>Arm 2 Sample size 75 mean 106.8 SD (15.2)</p> <p>Follow-up time 12 months</p> <p>Arm 1 Sample size 76 mean 102.5 SD (13.2)</p> <p>Arm 2 Sample size 86 mean 100.6 SD (14.6)</p> <p>Outcome Clinical adaptive test development quotient (CAT DQ)</p> <p>Follow-up time 30 months</p> <p>Arm 1 Sample size 72 mean 98.3 SD (8.7)</p> <p>Arm 2 Sample size 75 mean 98.1 SD (9)</p> <p>Follow-up time 12 months</p> <p>Arm 1 Sample size 76 mean 110 SD (10.8)</p> <p>Arm 2 Sample size 86 mean 109 SD (10)</p> <p>Outcome Gesell Gross Motor development quotient (DQ)</p> <p>Follow-up time 30 months</p> <p>Arm 1 Sample size 72 mean 102.4 SD (10.2)</p> <p>Arm 2 Sample size 75 mean 100.8 SD (11.4)</p> <p>Follow-up time 12 months</p> <p>Arm 1 Sample size 76 mean 99.5 SD (13.3)</p> <p>Arm 2 Sample size 86 mean 101.8 SD (13.8)</p>
<p>Jensen et al., 2010¹²⁰</p> <p>Study name: Unnamed Trial B</p> <p>Study dates: NR (<2010)</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry, Government</p>	<p>Study Population: Breast-feeding women</p> <p>Lactating enrolled 227</p> <p>Infants enrolled 230 Infants completers 119</p> <p>Lactating enrolled 227</p> <p>Lactating age: 31.5 years (5 years) 18 to 40</p> <p>Infant age: birth (NA) NA</p>	<p>Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age >=37 wk, infant birth weight between 2500 and 4200 g</p> <p>Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of</p>	<p>Start time: Infants birth</p> <p>Duration: Infants 4 months</p> <p>Arm 1: placebo</p> <p>Description capsule containing corn & soy oil</p> <p>Manufacturer Martek Biosciences</p> <p>Purity Data 50:50 mixture of soy and corn oils consisting, by weight, of 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18:2 n-6) and 3.9% a-linolenic acid (18:3 n-3)</p> <p>N-3 Composition.</p> <p>Dose 1 capsule</p> <p>Blinding capsules were identical</p>	<p>Outcome Development test of Visual-Motor Integration</p> <p>Follow-up time 5 years</p> <p>Arm 1 Sample size 56 mean 11.8 SD (1.8)</p> <p>Arm 2 Sample size 57 mean 11.6 SD (1.9)</p> <p>Outcome K-ABC hand movement</p> <p>Follow-up time 5 years</p> <p>Arm 1 Sample size 56 mean 9.02 SD (2.84)</p> <p>Arm 2 Sample size 59 mean 8.39 SD (2.55)</p> <p>Outcome McCarthy (leg coordination)</p> <p>Follow-up time 5 years</p> <p>Arm 1 Sample size 56 mean 10.7 SD (1.9)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Follow-up: 5 years ¹²¹ Follow-up article(s) ¹²¹	Race of Mother: NR (NR)	the infant	ALA 3.9% Arm 2: omega 3 capsule Description high-DHA algal triglyceride capsule Brand name DHASCO Manufacturer Martek Purity Data by weight, 44% saturated fatty acids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n-6) and 41.7% DHA (22:6n-3) Dose 1 capsule DHA 200 mg	Arm 2 Sample size 59 mean 10.6 SD (1.5) Outcome Purdue pegboard test (dominant hand) Follow-up time 5 years Arm 1 Sample size 57 mean 9.8 SD (2.7) Arm 2 Sample size 59 mean 9.6 SD (1.7) Outcome Purdue pegboard test (non-dominant hand) Follow-up time 5 years Arm 1 Sample size 57 mean 8.9 SD (2.7) Arm 2 Sample size 59 mean 8.9 SD (1.6)

Table 14. Observational Studies for Neurological development

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Guxens, et al., 2011¹²⁷</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Spain</p> <p>Funding source / conflict: Government</p> <p>Follow-up: ¹²⁸</p>	<p>Study Population: Breast-feeding women</p> <p>Pregnant enrolled 657 Pregnant completers 622</p> <p>Lactating enrolled 622 Lactating completers 582</p> <p>Infants enrolled 622 Infants completers 582 (319 with LCPUFA data)</p> <p>Lactating enrolled 622 Lactating completers 582</p> <p>Lactating age: 31.6 years (4.2 years)</p> <p>Infant age: 2 to 5 days post partum</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: age older than 16 years, intent to deliver at the reference hospital, singleton pregnancy</p> <p>Exclusion Criteria: no problems of communication, no assisted conception</p>
<p>Jordi Julvez, et al., 2014¹²⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Spain</p> <p>Funding source / conflict: Government</p> <p>Follow-up: ¹²⁷</p>	<p>Study Population: Breast-feeding women</p> <p>Pregnant enrolled 657 Pregnant completers 622</p> <p>Lactating enrolled 622 Lactating completers 582</p> <p>Infants enrolled 622 Infants completers 434</p> <p>Lactating enrolled 622 Lactating completers 582</p> <p>Lactating age: 31.6 years (4.2 years)</p> <p>Infant age: 2 to 5 days after birth</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: age older than 16 years, intent to deliver at the reference hospital, singleton pregnancy</p> <p>Exclusion Criteria: no problems of communication, no assisted conception</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Bernard, et al., 2013¹¹⁷</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: NR</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: Ref 20 in this article</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 2,002 Pregnant completers 1,882</p> <p>Infants enrolled 1,882 Infants completers 1,510</p> <p>Pregnant age: 29.2 years (at conception) (4.8 years) NR</p> <p>Infant age: < 24 weeks gestation (NR) NR</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: < 24 weeks amenorrhea</p> <p>Exclusion Criteria: multiple pregnancies, known diabetes before pregnancy, illiteracy, and intention to move outside the region in the next 3 years</p>
<p>Sun, et al., 2010¹¹⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Denmark</p> <p>Funding source / conflict: Government</p> <p>Follow-up: Unknown</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 65,754</p> <p>Infant age: birth</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: live-born singletons whose mothers provided information on fish intake from food frequency questionnaire</p> <p>Exclusion Criteria: children with missing information on maternal smoking and parity, children who died during the neonatal period, and children born to mothers with an unlikely high (>16,700 kJ/day) or low (<4200 kJ/day) intake of energy during pregnancy</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Valent, et al., 2013¹¹⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Italy</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 900 Pregnant completers 767</p> <p>Infants enrolled 767 Infants completers 632</p> <p>Pregnant age: 33.3 (4.3)</p> <p>Infant age: Birth</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Permanent residents of the study areas for at least 2 years, at least 18 years of age, and had no absence from the study area for more than 6 weeks during pregnancy, no history of drug abuse, no serious health problems or complications of pregnancy, and no twin gestation</p> <p>Exclusion Criteria: Preterm births (<37 weeks of gestational age), babies with congenital malformations or severe perinatal problems, and those with severe health problems that presented postnatally and potentially compromised their neurological development</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Bakker, et al., 2009¹¹⁹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Government</p> <p>Follow-up: ¹²⁹, refs 83 and 118 in original study</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 750 Infants withdrawals 444 Infants completers 306</p> <p>Pregnant age: 29.8 (4.1)</p> <p>Infant age: birth</p> <p>Race of Mother: White European (100)</p>	<p>Inclusion Criteria: 750 Caucasian children of 7 y old, born between December 1990 and January 1994 in the course of an earlier study on maternal and neonatal LCPUFA status and pregnancy outcome</p> <p>Exclusion Criteria: Not reported</p>
<p>Bouwstra, et al., 2006⁶⁷</p> <p>Study name: Groningen LCPUFA study</p> <p>Study dates: NR</p> <p>Study design: NR</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 6267</p> <p>Follow-up article(s) ^{61, 62, 63, 64, 65, 66, 68, 35}</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 317 Infants completers 269</p> <p>Infant age: 3 months (NR)</p> <p>Race of Mother: White European (100)</p>	<p>Inclusion Criteria: All infants were born at 37–42 wk of gestation, had a native West European origin, and were born between February 1997 and October 1999.</p> <p>Exclusion Criteria: children with a congenital disorder interfering with adequate functioning in daily life, children from multiple births, children whose mother did not master the Dutch language or had significant illness or disability, and adopted and fostered children</p>

Development of Visual Acuity

Key Points

- Prenatal Supplementation: Four RCTs found no effects of prenatal supplemental DHA on infant visual acuity, measured behaviorally or using VEP, at followup times ranging from 1 week to 6 months. (Studies were too dissimilar to pool).
 - Assessment of the associations between maternal and infant biomarkers following prenatal supplementation and visual acuity showed no association with maternal red blood cell DHA levels or maternal breast milk DHA but a significant association of earlier VEP development with cord blood DHA ($p=0.003$).
 - No prospective cohort studies were identified that assessed associations with visual function.
- Postpartum maternal supplementation: Three RCTs (two described in the original report) found no effect of postpartum maternal supplementation (of mothers with healthy term infants) with DHA on any measure of infant visual acuity among breastfed infants at 4 or 8 months, except for one study ($n=230$) that found a significant improvement in transient VEP amplitude at both time points, favoring DHA ($p<0.03$); this improvement was not seen at 5 years ($n=117$).
 - No association of infant plasma biomarkers with visual acuity was seen (one study). No studies assessed the association of maternal biomarkers
 - No observational studies were identified that assessed associations of postpartum maternal exposures with infant visual function.
- Supplementation of preterm infants with DHA and visual acuity was assessed in three RCTs (two in the original report and one identified for the current report; the intervention formula in two of the studies actually included small amounts of EPA). No differences were seen between groups at 2 months, but one study found a significant improvement in adjusted sweep VEP in boys at 4 months of age ($p=0.017$).
- Supplementation of preterm infants with DHA+AA and visual acuity was assessed in five RCTs identified for the original report and one RCT identified for the current report. Only one study reported a significant effect of supplementation, at 6 months. Pooling the new study with two studies from the original report showed no significant difference in VEP at 4 months of age, but pooling the new study with three studies from the original report showed a significant benefit for DHA+AA at 12 months using VEP ($-0.11[-0.20, -0.03]$).
- Supplementation of healthy term infants with DHA+AA showed inconsistent effects on visual acuity. Eight studies identified for the original report showed no differences at 2, 4, 6, 8 and 9 months; however four studies that assessed VEP at 12 months showed a significant pooled effect size in favor of DHA+AA ($p=0.01$). Among three studies identified for the current report, two showed significant differences in visual acuity at all time-points (up to 12 months), favoring DHA+AA, however the third study, a four year followup of a study reported in the original report, found no significant lasting effects of early supplementation of infant formula on visual acuity.
- A 2013 MA that pooled 16 RCTs (some included in the original report and some identified for the current report) to assess the effects of fish oil, DHA alone, or DHA plus AA on visual acuity of preterm and term infants at 2, 4, and/or 12 months found a small

but significant improvement in behaviorally measured visual acuity at 4 months among preterm infants, favoring n-3 FA (-0.04[-0.07, 0.00]), and a significant effect of DHA plus AA for term infants at 2, 4, and 12 months using VEP measures.

- Only one study assessed the association between infant biomarkers and visual acuity: This study found mixed associations between visual acuity, DHA, and AA, however at all time-points, better visual acuity was associated with lower n-6 FA to n-3 FA ratios.
- No prospective observational studies assessed the association of infant n-3FA exposures and visual acuity development.

Description of Included Studies

Visual acuity in the developing infant and child is assessed using two types of methods. Behavioral methods assess eye movement and head turning in response to the presentation of infants' preferred visual stimuli (patterns); visual acuity is defined as the highest spatial frequency that is distinguishable by the infant (according to the examiner). Electrophysiological methods include the measurement of visual evoked potentials (VEPs), which are physiological responses to these stimuli.

This section reports the findings of studies that assessed the effects of prenatal, postnatal maternal (breast milk), or postnatal infant PUFA supplementation or exposure on visual acuity development. Studies identified for this report are summarized in Table X and briefly summarized below.

Antepartum Maternal Supplementation with n-3 Fatty Acids and Infant Visual Acuity

The original report identified one RCT that assessed the effects of administering fish oil to pregnant women on infant photoreceptor function (by electroretinogram) at 1 week of age; this study found no effect.

DHA vs. placebo

For the current report, we identified four articles reporting on four RCTs that assessed the effect of supplementation of pregnant women with n-3 FA on infant visual acuity:^{32, 51, 98, 130} one article⁹⁸ reported on the same study in the original report that found no effect of DHA supplementation on photoreceptor function at 1 week. Enrollments ranged from 100⁹⁸ to 900.³² Studies were conducted in the UK, Canada, Australia, and Mexico.

All four studies administered supplemental DHA, two in the form of DHA-enriched fish oil,^{51, 98} and two from algal sources^{32, 130} Concentrations ranged from 0.2g/d to 1 gm/d. One study commenced supplementation at 15 weeks,⁹⁸ one began at 16 weeks,¹³⁰ and the two remaining studies began at midterm: all four continued supplementation until term..

Behavioral Measures

One study employed a BM, Teller visual acuity cards, to assess visual acuity in term infants at 60 days of age.¹³⁰

This study was not powered or designed to assess the effects of maternal DHA supplementation on infant visual acuity but to establish a range of visual acuity scores for infants born to women whose DHA intake was considered to be above requirements.¹³⁰ Visual acuity scores did not differ significantly between groups (p=0.3), however, in multivariate analysis, visual acuity scores were related only to sex and DHA intervention group.

Electrophysiological Measures

The remaining three studies employed various VEP measures to assess visual acuity at 0.25, 2.5, and 4 months,⁹⁸ 4 months,¹³¹ and 3 and 6 months.⁵¹ The study by Malcolm and colleagues (2003) found no difference between intervention groups in any VEP measure at birth or at 2.5 months and 4 months.⁹⁸ The study by Smithers and colleagues (2011) found no difference between intervention groups in mean sweep VEP acuity at 4 months in healthy full-term infants.⁵¹ The study by Stein and colleagues (2012) found no difference between intervention groups in any measure of VEPs at 3 and 6 months.³²

Maternal and Infant Biomarkers

Two of the four RCTs that assessed the effects of antepartum maternal supplementation with n-3 FA on children's visual acuity also assessed the association between biomarkers of exposure and visual acuity outcomes.

Innis and Friesen assessed the association between maternal red blood cell (RBC) ethanolamine phosphoglyceride (EPG) concentrations of DHA and infant visual acuity at 2 months of age. No difference was seen in Spearman rank correlation coefficients for either the DHA-supplemented or placebo groups, for girls ($\rho = 0.18, 0.10$) or boys ($\rho = -0.06, 0.07$).¹³⁰

Malcolm and colleagues assessed the association between cord RBC DHA maternal breast milk DHA, and VEP. They found a significant association between higher cord blood DHA at birth and earlier VEP development (pattern reversal peak latencies) ($p = 0.03$ for absolute levels and 0.004 for RBC DHA as a percent of total fatty acids). They observed no association between maternal breast milk DHA levels and VEPs.⁹⁸

No prospective cohort studies that assessed the association between maternal or infant biomarkers of n-3 FA status and visual acuity met our inclusion criteria.

Postpartum Maternal Supplementation with n-3 FA and Infant Visual Acuity

The original report identified two RCTs (one reported in an abstract) that examined the effects of postpartum maternal supplementation with increasing doses of n-3 FA (DHA) on the visual acuity of healthy term infants who were breastfed for at least 4 months (follow-up time). Doses ranged from 0.2g/d to 1.3g/d. Neither study showed a significant effect of DHA.

For the current report, we identified one new RCT that examined the effects of supplementing lactating mothers with n-3 FA on infant visual acuity.

DHA vs. Placebo

We identified two new articles reporting on one RCT that examined the effects of postpartum maternal DHA supplementation on infant visual acuity.^{120, 121}

Jensen and colleagues (the authors of the abstract summarized in the original report) randomly assigned 227 pregnant U.S. women who planned to breastfeed for at least 4 months to either algal DHA (approximately 0.2g/d) or placebo, to begin at 5 days postpartum and continue for 4 months.¹²⁰ Mothers of preterm or low birth weight infants were excluded. Compliance with the supplement was 95 percent to 100 percent. Visual acuity was assessed at 4 and 8 months of age in the 230 infants (including 3 twin pairs) as a secondary variable, using both BM and VEP. No significant differences were seen in visual acuity as assessed by BM at 4 (5.6 ± 0.71 vs. 5.3 ± 0.56 cycles/degree) or 8 months of age (12.3 ± 0.53 vs. 13.5 ± 0.57 cycles/degree) or sweep VEP at 4 months (9.4 ± 0.23 vs. 9.4 ± 0.21 cycles/degree). Transient VEP latency also did not differ between groups at 4 (124.8 ± 11.7 vs. 123.9 ± 10.6 milliseconds) or 8 months (115.1 ± 8.1 vs. 115.3 ± 10.5 milliseconds). Transient VEP amplitude was significantly lower in the infants of

DHA-treated mothers than in the infants of placebo-treated mothers at both 4 (28.9 ± 12.1 vs. 33.3 ± 12.4 μ Volts, $p < 0.03$) and 8 months (24.3 ± 8.9 vs. 27.9 ± 11.0 μ V, $p < 0.03$).

A subsequent article reported on visual acuity at 5 years of age in the same population ($n = 60$ children of DHA-supplemented mothers and 57 children of placebo mothers).¹²⁰ No differences were seen in visual acuity as measured by BM (Bailey Lovie visual acuity for both right and left eyes) between the groups (52.6 ± 4.6 vs. 51.6 ± 5.6 letters correct and 53.1 ± 4.7 vs. 52.1 ± 4.9 , respectively). VEP latency, amplitude, and sweep VEP acuity also showed no significant differences between treatment groups (110.3 ± 8.1 vs. 108.0 ± 6.5 msec; 39.6 ± 13.7 vs. 45.3 ± 18.0 μ Volts; 11.9 cycles/degree ± 0.3 octaves vs. 11.8 ± 0.3 octaves, respectively).

Maternal and Infant Biomarkers

Jensen and colleagues assessed the association between infant plasma phospholipid DHA and visual acuity and found no association (data not reported).¹²¹

Infant Formula Supplementation with n-3 FA and Visual Acuity in Preterm Infants

The original report identified nine RCTs that examined the effects of supplementing preterm or term formula with n-3 FA with or without breast feeding on visual acuity in preterm infants; the studies dated from 1992 to 2002. Duration of supplementation ranged from $\frac{3}{4}$ month to 12 months. Followups ranged from 2 months to 12 months: in some studies, the intervention ended several months before followup assessment. Two RCTs assessed the use of formula supplemented with DHA alone, 5 RCTs assessed the use of formula supplemented with DHA plus AA (or DHA plus AA plus a very small quantity of EPA), and the remainder used some combination of DHA, EPA, and ALA. Across the nine studies, outcomes were mixed: five studies reported a positive effect of some combination of n-3 FA on a visual acuity outcome, whereas four reported no effects (the intervention in three of these four studies was 2 months or less).

We also identified a 2013 meta-analysis of 16 studies that randomized term or preterm infants within one month of birth to infant formula supplemented with LC-PUFA (DHA or DHA plus AA) to assess the effects on visual acuity at 2, 4, and or 12 months of age. BM outcomes were analyzed separately from VEP outcomes. This meta-analysis included six of the studies of preterm infants identified in the original report, seven of the studies of term infants identified for the original report, and two of the three studies of term infants identified for the current report.^{132, 133}

Below we report the outcomes of the quantitative analysis in the original report, the results of the 2013 meta-analyses, and the results of newly identified studies.

DHA vs. Placebo

The original report identified two RCTs that compared the effects of supplementing preterm or term infant formula with DHA vs. placebo on visual acuity outcomes of healthy preterm infants, as assessed using BM. One RCT assessed acuity at 0, 2, 4, 6, and 9 months, and the other at 2 and 4 months. The formula employed in one of the two RCTs actually contained more EPA than DHA and the intervention duration was 9 months; the formula employed in the other intervention appears to have contained only DHA, but the intervention duration was only 1 month. No differences in visual acuity between treatment groups were observed at any time (effect sizes were pooled at 2 and 4 months).

One RCT identified for the current report randomized 143 preterm Australian infants (born at less than 33 weeks gestation) and their mothers to a supplement that contained DHA (29.5 percent of total fatty acids), EPA (6.5 percent), and a small amount of AA (1.8%) in the form of tuna fish oil or to a preterm formula that contained soy oil; the concentration of DHA was intended to mimic that provided in utero.¹⁰⁰ Breastfeeding mothers consumed the oil for the group to which they were assigned (the proportion of infants who received some breastmilk did not differ significantly between groups). The intervention duration was from birth to the expected delivery date. Visual acuity was assessed by sweep VEP at 4 months corrected age (the primary outcome) and VEP latency at 2 and 4 months corrected age. Adjusted sweep VEP was significantly higher at 4 months in the group that received the fish oil-supplemented formula (-1.4[-2.6,-0.2] p=0.017). The effect was significant in boys (-2.1[-3.4, -0.9]) but not in girls (-0.8[-1.9, 0.4]). No differences were observed in any of the visual acuity outcomes at 2 months. Use of n-3 FA supplements prenatally was similar across both groups.

DHA plus AA vs. Placebo

The original report identified five RCTs that compared the effects of infant formula supplemented with DHA and AA to a control formula. Pooled analysis of studies that measured visual acuity using BM found no differences between groups at 0, 2, 3, 4, or 6 months. Two studies employed VEP to measure visual acuity: One of the studies reported significantly improved visual acuity at 6 months, and pooled assessment of the outcomes of the two studies at 4 months showed no difference.

One RCT identified for the current report randomized 27 preterm infants (30 to 37 weeks gestation, >2000g birth weight) in Taiwan to a DHA (0.05%)- and AA(0.1%)-supplemented infant formula or the same formula without LC-PUFA.¹²⁶ The intervention duration was 6 months. No significant differences were observed in visual acuity between the intervention and control groups, measured by VEP or BM, at 4 or 6 months.

The 2013 systematic review described above¹³⁴ pooled four studies identified in the original report that assessed the effect of fish oil or DHA plus AA on visual acuity using BM at 2 months: The pooled standardized mean difference (SMD) was not significant (-0.04[-0.11, 0.03]). The 2013 review also pooled the newly identified study by Fang and colleagues¹²⁶ with six studies identified for the original report that assessed the effects of fish oil or DHA plus AA on visual acuity using BM at 4 months: The pooled SMD showed a small but significant improvement in visual acuity (-0.04[-0.07, 0.00]). However, pooling the new study with two of the studies identified for the original report that assessed VEP at 4 months of age showed a SMD that was not significant (-0.12[-0.29, 0.05]). Pooling three studies identified for the original report that assessed visual acuity using BM at 12 months also showed no significant benefit (SMD 0.02[-0.03, 0.07]) but pooling four studies that assessed visual acuity using VEP at 12 months showed a significant benefit for DHA plus AA (-0.11[-0.20, -0.03]).

Infant Formula Supplementation with n-3 FA and Visual Acuity in Term Infants

The original report identified 13 RCTs that examined the effects of supplementing infant formula with various combinations of n-3 and n-6 FA on visual acuity of term infants. Across the 13 RCTs, effects of supplementation on visual acuity were mixed. The 2013 meta-analysis also assessed the effects of n-3 FA with or without AA on visual acuity in term infants at 2, 4, and 12 months, with mixed results.

DHA vs. Placebo

The original report conducted a pooled analysis of two studies that compared infant formula supplemented with DHA on BM of visual acuity and found no significant benefit at 2, 4, 6, 9, or 12 months. Pooled analysis of three RCTs that used VEP to assess visual acuity also showed no effects at 2, 4, 6, 8, 9, or 12 months.

We identified one RCT that was not included in the original report or in the 2013 meta-analysis.¹³³ A 2007 article reported on a 4-year followup to a 1993-1995 RCT that randomized 79 healthy term U.S. infants within the first 5 days of life to 4 months of microalgal DHA, DHA plus microfungal AA, or a control formula.¹³⁵ At one year of followup, infants supplemented with DHA had shown significantly better visual acuity than the control group (as measured by sweep VEP), at 1.5, 4 and 12 months of age but not at 6 months.¹³⁵ Of the 79, 52 were available for followup visual acuity assessment at 4 years using a BM. At 4 years, the DHA group showed significantly better right-eye visual acuity than did the controls; the DHA group did not differ significantly from the DHA plus AA group or from a breast fed reference standard group. Left-eye visual acuity did not differ significantly among the groups.

DHA plus AA vs. Placebo

The original report pooled the results of three RCTs, which showed a significant improvement in visual acuity with DHA plus AA supplementation at 2 months, as measured using BM ($p < 0.01$) but not at 4 months or older (outcomes at 6, 9, and 12 months were reported in only one or two studies each). Similarly, the 2013 systematic review pooled the results of four RCTs with outcomes reported at 2 months and found a significant improvement in visual acuity as measured using BM (MSD -0.12[-0.20, -0.05]), whereas pooling four studies with BM outcomes reported at 4 months and four studies with outcomes reported at 12 months showed no significant effects of the interventions.

The original report also pooled eight RCTs that assessed visual acuity using VEP and found no effects of n-3 FA and AA at 2, 4, 6, 8, and 9 months; however pooling four studies that reported VEP outcomes at 12 months showed significant improvement ($p = 0.01$). The 2013 meta-analysis pooled four studies that reported outcomes at 2 months and found significant improvement in visual acuity (SMD -0.08[-0.14, -0.03]). Pooling seven studies that reported outcomes at 4 months also showed a significant effect for DHA plus AA (SMD -0.06[-0.12, -0.01]), as did pooling four studies that reported VEP outcomes at 12 months (SMD -0.11[-0.20, -0.03]).

Three new RCTs, two of which were included in the 2013 meta-analysis, were identified for the current report. These studies are described here briefly (the first two were included in the 2013 meta-analysis; the third was not).

A 2005 RCT by Birch and colleagues randomized 103 healthy term U.S. infants in the first 5 days of life to a standard infant formula or a formula fortified with DHA (0.36% of total fatty acids) and AA (0.72% of total fatty acids).¹⁰⁷ The experimental diets were given through 12 months and solid foods were not introduced before 4 months. Visual function was assessed by sweep VEP, random dot stereoacuity, and electroretinography at 1.5 months, 4 months, 9 months, and 12 months. VEP acuity was significantly greater in the intervention group at all time-points, with the overall differences corresponding to slightly more than a one-line difference in reading a standard eye chart.

A 2010 RCT by the same researchers, the DIAMOND Study, randomized healthy term U.S. infants born at one of 7 hospitals at two study sites to one of four intervention groups within 9 days of birth (study sites differed significantly by race, ethnicity, parental education, and

gestational length).¹³² Children who had received breast milk were excluded. Three of the intervention groups received a standard formula fortified with 0.32% DHA (0.017g/100kcal), 0.64% DHA (0.034g/100 kcal), or 0.96% DHA; all intervention formulae also included 0.64% fatty acids as AA (0.034 g/100kcal). The control group received the standard formula with no DHA or AA. As in the 2005 study, the intervention was continued for 12 months and no other foods were introduced prior to 4 months of age. Visual acuity was assessed by sweep VEP at 1.5, 4, 6, 9 and 12 months. Control infants had poorer visual acuity than the intervention groups at all time-points; visual acuity did not differ among the active intervention groups at any time. Significant differences in acuity and response to the interventions were noted between study sites, with the control group at one site showing significantly worse visual acuity than the control group at the other site but the interventions groups at the first site showing significantly better response to the interventions than the intervention groups at the second site.

The 2007 4-year follow-up RCT described in the previous subsection on DHA-only interventions found that right-eye visual acuity in the children who received formula with DHA plus AA was better, but not significantly better, than that of the children who had received the control formula. Left-eye visual acuity did not differ significantly among the groups.¹³³ Infants treated with formula containing DHA plus AA had shown significantly better visual acuity than the control group (as measured by sweep VEP), at 1.5, 4 and 12 months of age but not at 6 months.¹³⁵

Infant biomarkers

One RCT identified for the current study assessed the association between infant red blood cell lipids and sweep VEP acuity.¹⁰⁷ This study, which compared visual acuity over 12 months between infants who received a formula containing DHA plus AA and those receiving a control formula, found that at 4 months, better visual acuity was associated with higher DHA concentrations but not with AA, ALA, or LA concentrations. At 9 months, better visual acuity was associated with higher DHA and AA levels at both 4 months and 9 months. At 1 year, better visual acuity was associated with higher DHA at 4 months and 9 months and with higher AA at 9 months. At all time-points, better visual acuity was also associated with a lower n-6 to n-3 ratio and higher DHA to n-6 DPA.

Table 15. RCTs for Visual function

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Birch et al., 2007¹³³</p> <p>Study name: Birch</p> <p>Study dates: 1993-1999</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up: 4 years 9412/11598</p> <p>Follow-up article(s) ^{136, 137}</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 79+40BF Infants completers 52+32BF</p> <p>Infant age: birth (0-5 days)</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: All participants were born at 37 to 40 weeks postmenstrual age. Only singleton births with birthweights appropriate for gestational age</p> <p>Exclusion Criteria: family history of milk-protein allergy, genetic or familial eye disease (e.g. hereditary retinal disease, strabismus), vegetarian or vegan maternal dietary patterns, maternal metabolic disease, anemia, or infection, presence of a congenital malformation or infection, jaundice, perinatal asphyxia, meconium aspiration, and any perinatal event which resulted in placement of the infant in the neonatal intensive care unit</p>	<p>Start time: Infants birth (0-5 days)</p> <p>Duration: Infants 17 weeks</p> <p>Arm 1: Control Description standard infant formula without added n-3 FA Brand name Enfamil with Iron Manufacturer Mead Johnson Nutritionals Active ingredients linoleic acid: 15% of total fats N-3 Composition. ALA 1.5% of total fats</p> <p>Arm 2: DHA Description infant formula fortified with DHA Brand name Enfamil with Iron, supplemented with DHASCO Manufacturer Formula: Mead Johnson; DHA: Martek Biosciences Active ingredients linoleic acid: 15% of total fats ALA 1.5% DHA 0.36%</p> <p>Arm 3: DHA+ARA Description infant formula fortified with DHA and ARA Brand name Enfamil with Iron, fortified with DHASCO and ARASCO Manufacturer Formula: Mead-Johnson; DHA, ARA: Martek Biosciences Active ingredients linoleic acid 15% ALA 1.5% DHA 0.36% AA 0.72%</p>	<p>Outcome Visual acuity Left Eye Follow-up time 4 years Arm 1 Sample size 19 mean 0.052 SE (1.6E-2) Arm 2 Sample size 16 mean 0.016 SE (0.02) Arm 3 Sample size 17 mean 0.026 SE (0.02)</p> <p>Outcome Visual acuity Right Eye Follow-up time 4 years Arm 1 Sample size 19 mean 0.076 SE (0.02) Arm 2 Sample size 16 mean 0.023 SE (1.9E-2) Arm 3 Sample size 17 mean 0.034 SE (0.02)</p>
<p>Smithers et al., 2008¹⁰⁰</p> <p>Study name: DINO</p> <p>Study dates: 2001-2004</p> <p>Study design: Trial randomized parallel</p>	<p>Study Population: Preterm infants</p> <p>Lactating enrolled unclear</p> <p>Infants enrolled 143 Infants completers 125</p>	<p>Inclusion Criteria: infants born_x0001_33 wk gestation at the Women's and Children's Hospital of the Child, Youth, and Women's Health Service, Adelaide, Australia, between April</p>	<p>Start time: Lactating approximately 5 days after birth Infants approximately 5 days after birth</p> <p>Duration: Lactating to estimated due date Infants to estimated due date</p> <p>Arm 1: Control group Description Placebo capsules and/or formula</p>	<p>Outcome Visual evoked potential acuity Follow-up time 2 months (corrected age) Arm 1 Sample size 61 mean 5.6 SD (2.4) Arm 2 Sample size 54 mean 5.6 SD (2.4)</p> <p>Follow-up time 4 months (corrected age) Arm 1 Sample size 51 mean 8.2 SD (1.8) Arm 2 Sample size 44 mean 9.6 SD (3.7)</p> <p>Outcome Visual evoked potential latency:</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Location: Australia</p> <p>Funding source / conflict: Manufacturer supplied product</p> <p>Follow-up: 2 months, 4 months 4266, 7357</p> <p>Follow-up article(s)^{111, 112, 113, 101, 114}</p>	<p>Lactating enrolled unclear</p> <p>Mother age: Control: 31 Treatment: 29 (Control: 6 Treatment: 6)</p> <p>Infant age: 5 days (control) (mean gestational age at birth 29.4 weeks) 6 days (Treatment) (3)</p> <p>Race of Mother: NR (NR)</p>	<p>2001 and September 2003</p> <p>Exclusion Criteria: Infants with major congenital or chromosomal abnormalities, lactating mothers for whom tuna oil was contraindicated (women with blood-thinning disorders or currently taking anticoagulants)</p>	<p>Active ingredients Linoleic acid 53.4% of fatty acids N-3 Composition. Dose 6 500-mg capsules per day to mothers Blinding The soy and tuna oil capsules were identical in size, color, and shape ALA 5.9% of total fatty acids Arm 2: Treatment Description DHA supplemented breastfeeding mothers and/or formula Active ingredients Linoleic acid 2.7% of fatty acids Dose 6 capsules or formula ad lib ALA 0.4% total FA DHA 29.5% total FA EPA 6.5% total FA AA 1.8% total FA</p>	<p>48 min of arc Follow-up time 4 months (corrected age) Arm 1 Sample size 67 mean 138 SD (23) Arm 2 Sample size 58 mean 135 SD (23) Outcome Visual evoked potential latency: 69 min of arc Follow-up time 2 months (corrected age) Arm 1 Sample size 66 mean 200 SD (29) Arm 2 Sample size 58 mean 193 SD (27) Follow-up time 4 months (corrected age) Arm 1 Sample size 67 mean 131 SD (21) Arm 2 Sample size 58 mean 129 SD (20) Outcome Visual evoked potential latency: 96 min of arc Follow-up time 2 months (corrected age) Arm 1 Sample size 66 mean 188 SD (27) Arm 2 Sample size 58 mean 182 SD (24)</p>
<p>Smithers et al., 2011⁵¹</p> <p>Study name: DOMInO</p> <p>Study dates: enrollment from June 2007 to August 2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations</p> <p>Follow-up: 4 months 3069, 3170, 4404, 4875, 9417</p> <p>Follow-up article(s)^{34, 48,}</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Infants enrolled 185 Infants completers 182</p> <p>Pregnant age: Tx = 29.5 years, Placebo = 28.7 years (Tx = 5.5 years, Placebo = 5.4 years) NR</p> <p>Infant age: (NA) NA</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: singleton pregnancies at less than 21 weeks' gestation</p> <p>Exclusion Criteria: already taking a prenatal supplement with DHA, fetus had a known major abnormality, mother had a bleeding disorder in which tuna oil was contraindicated, taking anticoagulant therapy, history of drug or alcohol abuse, participating in another fatty acid trial, unable to give written informed consent, or English was not the main language spoken at home</p>	<p>Start time: Pregnant 18 to 21 weeks gestation</p> <p>Duration: Pregnant until birth</p> <p>Arm 1: placebo Description vegetable oil capsule Manufacturer Efamol Dose 3 500 mg capsules Blinding similar in size, shape, and color Arm 2: Omega 3 supplement Description fish oil capsule Brand name Incromega Manufacturer Croda Chemicals Dose 3 500 mg capsules DHA 800/3 mg EPA 100/3 mg</p>	<p>Outcome VEP Latency: 20 min of arc Follow-up time 4 months Arm 1 Sample size 93 mean 133 SD (14) Arm 2 Sample size 89 mean 133 SD (15) Outcome VEP Latency: 48 min of arc Follow-up time 4 months Arm 1 Sample size 93 mean 121 SD (12) Arm 2 Sample size 89 mean 121 SD (10) Outcome VEP Latency: 69 min of arc Follow-up time 4 months Arm 1 Sample size 93 mean 116 SD (9) Arm 2 Sample size 89 mean 115 SD (8) Outcome VEP acuity (adjusted) Follow-up time 4 months Arm 1 Sample size 93 mean 8.55 SD (1.97) Arm 2 Sample size 89 mean 8.37 SD (1.97) Outcome VEP acuity (unadjusted) Follow-up time 4 months Arm 1 Sample size 93 mean 8.55 SD (1.86) Arm 2 Sample size 89 mean 8.37 SD (2.11)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
49, 50, 52, 53, 3				
<p>Birch et al., 2010¹³²</p> <p>Study name: Diamond</p> <p>Study dates: 2003-2006</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry, Some authors employed by industry (companies that make the supplements)</p> <p>Follow-up article(s) ^{138, 139}</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 343 Infants completers 244</p> <p>Pregnant age: NR</p> <p>Mother age: NR</p> <p>Infant age: 1-9 days</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: Healthy term formula-fed, singleton-birth infants born in any of 5 hospitals</p> <p>Exclusion Criteria: Infants who had received human milk within 24 h of randomization or who had diseases or congenital abnormalities likely to interfere with normal growth and development or with the normal maturation of visual or cognitive function, poor formula intake, or known or suspected intolerance to cow milk infant formula were excluded from the study. Also excluded were infants born to mothers with chronic illness, such as HIV disease, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or substance abuse</p>	<p>Start time: Infants 4-9 days of age</p> <p>Duration: Infants 12 months</p> <p>Arm 1: Control Brand name Enfamil with IRon Manufacturer Mead-Johnson Nutrition, Evansville IN</p> <p>Arm 2: 0.32% DHA Brand name Enfamil LIPIL Manufacturer Mead-Johnson; DHA and ARA from algal and fungal oils manufactured by Martek Biosciences N-3 Composition 17mg DHA/100kcal Dose not specified Blinding not specified DHA 0.32% or 17mg/100kcal AA 0.64% FA or 34mg/100kcal</p> <p>Arm 3: 0.64% DHA Brand name not specified Manufacturer not specified DHA 34mg/100kg AA 0.64% FA or 34mg/100kcal</p> <p>Arm 4: 0.96% DHA Brand name not specified Manufacturer not specified DHA 51mg/100kg AA 0.64% FA or 34mg/100kcal</p>	data only reported on graph
<p>Birch et al., 2005¹⁰⁷</p> <p>Study name: NR</p> <p>Study dates: Not reported</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 103 Infants completers 86</p> <p>Pregnant age: 31 years (4 years)</p> <p>Infant age: 3.6 _x0004_days (1.3 days)</p>	<p>Inclusion Criteria: All were born at 37– 40 wk after conception. Only singleton births with birth weight appropriate for gestational age</p> <p>Exclusion Criteria: Family history of milk protein allergy, genetic or familial eye disease,</p>	<p>Start time: Infants 1-5 days</p> <p>Duration: Infants 52 wks</p> <p>Arm 1: Control Description Commercial infant formula Brand name Enfamil with Iron Manufacturer Mead Johnson Nutritionals, Evansville, IN</p> <p>Active ingredients Linoleic acid-8.48g/L (14.6%); 14.7 g protein/L, 37.5 g fat/L, 69.0 g carbohydrate/L</p>	data only reported on graph

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Industry, Government, Manufacturer supplied product	1-5 days Race of Mother: NR	vegetarian or vegan maternal dietary patterns, maternal metabolic disease or infection, jaundice, perinatal asphyxia, meconium aspiration, or any perinatal event that resulted in placement of the infant in the neonatal intensive care unit.	N-3 Composition. Blinding Each diet was masked by 2 color and 2 number codes, for a total of 4 possible diet assignments. The randomization schedule had random-length blocks (block length varied from 6 to 12) and was provided in individual sealed envelopes to the study site. ALA 1.5% of total fatty acids Arm 2: LCPUFA-supplemented formula Description Commercial formula supplemented with LCPUFA Brand name Enfamil with Iron plus DHASCO and ARASCO Manufacturer Formula: Mead Johnson; DHA+ARA: Martek Biosciences Active ingredients 15% linoleic acid, 14.7 g/L protein, 37.5 g/L fat, 69.0 g/L carbohydrate ALA 1.5% of total fatty acids DHA 0.36% of total fatty acids AA 0.72% of total fatty acids	
Fang et al., 2005 ¹²⁶ Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Taiwan Funding source / conflict: Manufacturer supplied product	Study Population: Preterm infants Infants enrolled 28 Infants withdrawals 1 Infants completers 27 Infant age: 1 week (mean gestation age 33 weeks) (0.5 week) NA Race of Mother: NR (100)	Inclusion Criteria: (1) A gestational age at birth between 30 and 37 weeks; (2) Normal fundus oculi; (3) Recruitment prior to commencement of feeding Exclusion Criteria: (1) Breast feeding; (2) A maternal history of infection, diabetes mellitus, gestational diabetes mellitus, cocaine or alcohol abuse, systemic diseases or if intrauterine growth retardation had been diagnosed during pregnancy; (3) Major congenital abnormality; (4) Severe	Start time: Infants 1 week after birth Duration: Infants 24 weeks Arm 1: placebo Description infant formula based on the composition of human milk Brand name Neoangelac Manufacturer Multipower Enterprise Corporation N-3 Composition. Dose Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months N-6 N-3 10:1 linoleic:linolenic Arm 2: Neoangelac Plus Description Neoangelac supplemented with Omega 3 Brand name Neoangelac Plus Manufacturer Multipower Enterprise Corporation Dose Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months DHA 0.05%	Outcome Hiding Heidi Analysis <100% Follow-up time 4 months Arm 1 2/11 (18%) Arm 2 5/16 (31%) Follow-up time 6 months Arm 1 10/11 (91%) Arm 2 16/16 (100%) Outcome Lea grating acuity card 1 or 2 cycles per degree Follow-up time 4 months Arm 1 8/11 (72%) Arm 2 16/16 (100%) Outcome Lea grating acuity card 2 or 4 cycles per degree Follow-up time 6 months Arm 1 8/11 (73%) Arm 2 15/16 (94%) Outcome Visual evoked potential Follow-up time 4 months Arm 1 Sample size 10 mean 0.36 SD (0.34) Arm 2 Sample size 14 mean 0.19 SD (0.27)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		intraventricular hemorrhage > grade 2; (5) Cystic periventricular leukomalacia; (6) Retinopathy of prematurity stage 2; (7) Bronchopulmonary dysplasia on radiographs or oxygen usage 28 days; (8) Body weight less than the third percentile; (9) Surgical intervention for necrotizing enterocolitis (10) Mechanical ventilation after achieving enteral intake > 110 kcal/kg per day; (11) A 5-min Apgar score < 7; (12) Administration of blood transfusion, blood products, or parenteral lipids with DHA or AA.	AA 0.10%	Follow-up time 6 months Arm 1 Sample size 10 mean 0.13 SD (0.22) Arm 2 Sample size 13 mean 0.1 SD (0.17)
Innis et al., 2008 ¹³⁰ Study name: NR Study dates: NR, <2008 Study design: Trial randomized parallel Location: Canada Funding source / conflict: Government, None, Manufacturer supplied product Follow-up: 60 days 7894	Study Population: Healthy pregnant women Pregnant enrolled NR Pregnant completers 135 Infants enrolled 135 Infants completers 134 Pregnant age: 33 years (0. 4 years) Infant age: 14 to 16 weeks gestation Race of Mother: White European (72%)	Inclusion Criteria: 14 –16 wk gestation, not taking any lipid supplement, no complications likely to affect maternal or fetal metabolism or fetal development, expected to deliver one full-term infant Exclusion Criteria: NR	Start time: Pregnant 16 weeks gestation Infants 16 weeks gestation Duration: Pregnant to birth Infants to birth Arm 1: placebo Description corn oil / soybean oil capsule Manufacturer Martek Biosciences, Columbia, MD) N-3 Composition. Dose 2 capsules Blinding identical capsules, containing an orange flavor to assist in further blinding Maternal conditions ALA 40 mg Other dose 1 LA 265 mg Current smoker 2/67 Arm 2: DHA supplement Description capsule containing 200 mg DHA Manufacturer Martek Biosciences, Columbia, MD)	Outcome Teller Acuity Card procedure (visual acuity) Follow-up time 60 days Arm 1 Sample size 68 mean 2.42 SD (0.63) Arm 2 Sample size 67 mean 2.6 SD (0.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Follow-up article(s) ¹⁴⁰			Dose 2 capsules Maternal conditions DHA 200 mg/g Current smoker 0/68	
<p>Malcolm et al., 2003⁹⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Trial randomized parallel</p> <p>Location: NR</p> <p>Funding source / conflict: NR</p>	<p>Study Population: NR</p> <p>Pregnant enrolled 100 Pregnant withdrawals 37 Pregnant completers 63</p> <p>Infants enrolled 60 Infants withdrawals 5 Infants completers 55</p> <p>Infant age: 279.6 (8.5)</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: d women who were expected to deliver their infants at term and planned to feed them on breast and/or formula milk</p> <p>Exclusion Criteria: diabetes, twin pregnancies, pre-eclamptic toxemia, a past history of abruption or postpartum haemorrhage, allergy to fish products, a thrombophilic tendency, or who were receiving drugs that affect thrombocyte function (non-steroidal anti-inflammatories)</p>	<p>Start time: Pregnant week 15 Infants birth</p> <p>Duration: Pregnant birth</p> <p>Arm 1: Placebo Description contained 323 mg sunflower oil with high levels of oleic acid and was free of any significant amounts of LCPUFAs or their precursors Manufacturer R P Scherer Limited (Swindon, Wiltshire, UK) N-3 Composition. Dose 323 mg per capsule * 2 Blinding e identical in appearance and could not be identified on the basis of scent or taste Total N-3 0</p> <p>Arm 2: DHA Description f a blended fish oil, Marinol D40, and contained 100 mg DHA in 323 mg oil per capsule Manufacturer R P Scherer Limited (Swindon, Wiltshire, UK) Dose 323 mg capsule * 2 DHA 200 mg EPA .64 mg (estimated based on the FA composition)</p>	<p>Outcome Peak latencies of major components of the transient flash visual evoked potential waveform: N1 Follow-up time 50 weeks (corrected age) Arm 1 Sample size 18 mean 58.1 SD (21.4) Arm 2 Sample size 19 mean 54.7 SD (16.2) Follow-up time 66 weeks (corrected age) Arm 1 Sample size 24 mean 57.3 SD (10.7) Arm 2 Sample size 23 mean 61.5 SD (5.4) Follow-up time birth Arm 1 Sample size 4 mean 74.8 SD (16.8) Arm 2 Sample size 5 mean 62.2 SD (3.8) Outcome Peak latencies of major components of the transient flash visual evoked potential waveform: N2 Follow-up time 50 weeks (corrected age) Arm 1 Sample size 28 mean 112.8 SD (46.5) Arm 2 Sample size 24 mean 128.9 SD (47.9) Follow-up time 66 weeks (corrected age) Arm 1 Sample size 26 mean 122.1 SD (33.7) Arm 2 Sample size 25 mean 128.5 SD (30.3) Follow-up time birth Arm 1 Sample size 22 mean 149.9 SD (28) Arm 2 Sample size 27 mean 153.5 SD (28.9) Outcome Peak latencies of major components of the transient flash visual evoked potential waveform: N3 Follow-up time 50 weeks (corrected age) Arm 1 Sample size 20 mean 277.3 SD (49.4) Arm 2 Sample size 14 mean 241.8 SD</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				<p>(49.8) Follow-up time 66 weeks (corrected age) Arm 1 Sample size 15 mean 209.2 SD (38.2) Arm 2 Sample size 11 mean 228.9 SD (55.9) Follow-up time birth Arm 1 Sample size 27 mean 298.4 SD (52.8) Arm 2 Sample size 26 mean 292.2 SD (58.2) Outcome Peak latencies of major components of the transient flash visual evoked potential waveform: P1 Follow-up time 50 weeks (corrected age) Arm 1 Sample size 22 mean 84.2 SD (22.5) Arm 2 Sample size 23 mean 80.3 SD (21.1) Follow-up time 66 weeks (corrected age) Arm 1 Sample size 26 mean 76.5 SD (19.5) Arm 2 Sample size 25 mean 80.1 SD (15.8) Follow-up time birth Arm 1 Sample size 5 mean 107.8 SD (11.8) Arm 2 Sample size 9 mean 101 SD (13.6) Outcome Peak latencies of major components of the transient flash visual evoked potential waveform: P2 Follow-up time 50 weeks (corrected age) Arm 1 Sample size 26 mean 162.5 SD (26.5) Arm 2 Sample size 21 mean 164.2 SD (29.9) Follow-up time 66 weeks (corrected age) Arm 1 Sample size 19 mean 152.5 SD (43.6) Arm 2 Sample size 12 mean 150.6 SD (33) Follow-up time birth Arm 1 Sample size 27 mean 201.8 SD (33.3)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2 Sample size 28 mean 201.9 SD (28.4)
<p>Stein et al., 2012³²</p> <p>Study name: POSGRAD</p> <p>Study dates: Feb 2005-Feb 2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: NR</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 3364</p> <p>Follow-up article(s) ^{31, 72}</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 1094 Pregnant withdrawals 63 Pregnant completers 900</p> <p>Pregnant age: 26.3 (4.6-4.8)</p> <p>Infant age: 39.1 (1.7-1.8)</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: Singleton live births without congenital anomalies</p> <p>Exclusion Criteria: 3364: high risk pregnancy, (history and prevalence of pregnancy complications, including abruptio placentae, preeclampsia, pregnancy-induced hypertension, any serious bleeding episode in the current pregnancy, and physician referral); lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplement, or chronic use of certain medication(eg. epilepsy medications)</p>	<p>Start time: Pregnant 18-22 wk</p> <p>Duration: Pregnant to birth</p> <p>Arm 1: Placebo Description A mixture of coin and soy oil Manufacturer Martek Biosciences Blinding "Participants and members of the study team were unaware of the treatment scheme throughout the intervention period of the study"</p> <p>Arm 2: DHA Description DHA 400 mg/d Manufacturer Martek Biosciences Dose 2 capsule per day DHA 2*200mg</p>	<p>Outcome Visual evoked potential: Amplitude P</p> <p>Follow-up time 3 months</p> <p>Arm 1 Sample size 342 mean 8.14 SD (6.04)</p> <p>Arm 2 Sample size 337 mean 7.75 SD (5.97)</p> <p>Follow-up time 6 months</p> <p>Arm 1 Sample size 342 mean 11.3 SD (6.9)</p> <p>Arm 2 Sample size 337 mean 11.2 SD (7.2)</p> <p>Outcome Visual evoked potential: Latency N1</p> <p>Follow-up time 3 months</p> <p>Arm 1 Sample size 342 mean 93.9 SD (17.1)</p> <p>Arm 2 Sample size 337 mean 94.2 SD (16.3)</p> <p>Follow-up time 6 months</p> <p>Arm 1 Sample size 342 mean 91.9 SD (15.1)</p> <p>Arm 2 Sample size 337 mean 90.5 SD (14.6)</p> <p>Outcome Visual evoked potential: Latency N3</p> <p>Follow-up time 3 months</p> <p>Arm 1 Sample size 342 mean 157.1 SD (24.1)</p> <p>Arm 2 Sample size 337 mean 154.8 SD (23.8)</p> <p>Follow-up time 6 months</p> <p>Arm 1 Sample size 342 mean 154.9 SD (20.2)</p> <p>Arm 2 Sample size 337 mean 154.2 SD (19.9)</p> <p>Outcome Visual evoked potential: Latency P1</p> <p>Follow-up time 3 months</p> <p>Arm 1 Sample size 342 mean 126.3 SD (18.3)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2 Sample size 337 mean 125.8 SD (17.5) Follow-up time 6 months Arm 1 Sample size 342 mean 123.5 SD (14.3) Arm 2 Sample size 337 mean 122.7 SD (14.6)
<p>Jensen et al., 2005¹²¹</p> <p>Study name: Unnamed Trial B</p> <p>Study dates: <2004</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up article(s)¹²⁰</p>	<p>Study Population: Breast-feeding women</p> <p>Lactating enrolled 227 Lactating completers 174</p> <p>Infants enrolled 230 Infants completers 177</p> <p>Lactating enrolled 227 Lactating completers 174</p> <p>Lactating age: 31.5 years (5 years) 18-40</p> <p>Infant age: birth (NA) NA</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age ≥ 37 wk, infant birth weight between 2500 and 4200 g</p> <p>Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant</p>	<p>Start time: Lactating 5 days after delivery Infants 5 days after birth</p> <p>Duration: Lactating 4 months Infants 4 months</p> <p>Arm 1: placebo Description capsule containing corn & soy oil Manufacturer Martek Biosciences Purity Data 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18: 2n_x0001_6), and 3.9% _x0001_-linolenic acid (18:3n_x0001_3) N-3 Composition. Dose 1 capsule Blinding identical capsules ALA 56.3% linoleic acid (18: 2n_x0001_6), 3.9% _x0001_-linolenic acid (18:3n_x0001_3) Total N-3 57.2% Arm 2: DHA algal triacylglycerol (DHASCO) Description DHA capsule Brand name DHASCO Manufacturer Martek Biosciences Purity Data 44% saturated fatty acids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n_x0001_6), and 41.7% DHA (22:6n-3) by weight N-3 Composition 0.8% linoleic acid (18:2n_x0001_6), 41.7% DHA (22:6n_x0001_3) Dose 1 capsule ALA 0.8% DHA 200 mg Total N-3 42.5%</p>	<p>Outcome Sweep VEP Follow-up time 4 months Arm 1 Sample size 79 mean 9.4 SD (0.21) Arm 2 Sample size 81 mean 9.4 SD (0.23) Outcome Teller Acuity Card procedure Follow-up time 4 months Arm 1 Sample size 77 mean 5.3 SD (0.56) Arm 2 Sample size 70 mean 5.6 SD (0.71) Follow-up time 8 months Arm 1 Sample size 73 mean 13.5 SD (0.57) Arm 2 Sample size 74 mean 12.3 SD (0.53) Outcome Visual evoked potential amplitude Follow-up time 4 months Arm 1 Sample size 82 mean 33.3 SD (12.4) Arm 2 Sample size 86 mean 28.9 SD (12.1) Follow-up time 8 months Arm 1 Sample size 74 mean 27.9 SD (11) Arm 2 Sample size 79 mean 24.3 SD (8.9) Outcome Visual evoked potential latency Follow-up time 4 months Arm 1 Sample size 82 mean 123.9 SD (10.6) Arm 2 Sample size 86 mean 124.8 SD (11.7) Follow-up time 8 months Arm 1 Sample size 74 mean 115.3 SD (10.5) Arm 2 Sample size 79 mean 115.1 SD (8.1)</p>
Jensen et al., 2010 ¹²⁰	Study Population: Breast-feeding women	Inclusion Criteria: maternal age between	Start time: Infants birth	intervention first 4 months; same trial as 3433 (later fu)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study name: Unnamed Trial B</p> <p>Study dates: NR (<2010)</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: 5 years ¹²¹</p> <p>Follow-up article(s) ¹²¹</p>	<p>Lactating enrolled 227</p> <p>Infants enrolled 230 Infants completers 119</p> <p>Lactating enrolled 227</p> <p>Lactating age: 31.5 years (5 years) 18 to 40</p> <p>Infant age: birth (NA) NA</p> <p>Race of Mother: NR (NR)</p>	<p>18 and 40 y, infant gestational age \geq37 wk, infant birth weight between 2500 and 4200 g</p> <p>Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant</p>	<p>Duration: Infants 4 months</p> <p>Arm 1: placebo Description capsule containing corn & soy oil Manufacturer Martek Biosciences Purity Data 50:50 mixture of soy and corn oils consisting, by weight, of 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18:2 n-6) and 3.9% α-linolenic acid (18:3 n-3) N-3 Composition. Dose 1 capsule Blinding capsules were identical ALA 3.9%</p> <p>Arm 2: omega 3 capsule Description high-DHA algal triglyceride capsule Brand name DHASCO Manufacturer Martek Purity Data by weight, 44% saturated fatty acids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n-6) and 41.7% DHA (22:6n-3) Dose 1 capsule DHA 200 mg</p>	<p>Outcome Bailey Lovie Acuity - left eye (number of letters correct) Follow-up time 5 years Arm 1 Sample size 57 mean 52.1 SD (4.9) Arm 2 Sample size 60 mean 53.1 SD (4.7) Outcome Bailey Lovie Acuity - right eye (number of letters correct) Follow-up time 5 years Arm 1 Sample size 58 mean 51.6 SD (5.6) Arm 2 Sample size 60 mean 52.6 SD (4.6) Outcome Sweep VEP acuity Follow-up time 5 years Arm 1 Sample size 55 mean 11.8 SD (0.3) Arm 2 Sample size 56 mean 11.9 SD (0.3) Outcome VEP Amplitude Follow-up time 5 years Arm 1 Sample size 56 mean 45.3 SD (18) Arm 2 Sample size 60 mean 39.6 SD (13.7) Outcome VEP Latency (30' check sizes) Follow-up time 5 years Arm 1 Sample size 56 mean 108 SD (6.5)</p>

Table 16. Observational studies for Visual function

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Keim, et al., 2012¹⁴¹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: US</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Breast-feeding women</p> <p>Pregnant enrolled 1,169 Pregnant completers 689</p> <p>Infants enrolled 408 Infants completers 358</p> <p>Pregnant age: NR NR</p> <p>Infant age: 20 weeks gestation NA</p> <p>Race of Mother: White European (79.1%)</p>	<p>Inclusion Criteria: health women at less than 20 weeks of pregnancy</p> <p>Exclusion Criteria: pregnant with multiple fetuses, unable to communicate in English, under age 16 years, no access to a telephone, intention to go elsewhere for future care or delivery</p>

Cognitive Development

Key Points

- Eight RCTs on supplementation of pregnant women were identified. (One was included in the previous AHRQ systematic review.) Due to heterogeneity of omega 3 content and outcome measurement, meta-analysis was not conducted. With the exception of a study that assessed infants at 14 weeks, studies reported no significant associations between supplementation and cognitive outcomes in offspring.
- Six RCTs, including two from the previous AHRQ review, reported on supplementation for lactating women. Due to heterogeneity of omega 3 content and outcome measurement, meta-analysis was not conducted. Associations between supplementation and cognitive outcomes in offspring were not significant in these studies.
- The previous AHRQ systematic review included six RCTs in pre-term infants that reported cognitive outcomes, while the current one identified six reports on five RCTs. Due to heterogeneity of interventions, populations, outcome measures, and timing, meta-analysis was not conducted. Results were inconsistent.
- Regarding full term infants, the previous AHRQ systematic view reported that 6 of 8 RCTs did not find a significant difference between intervention and placebo groups in the Bayley's MDI. The current review identified five reports on four RCTs. One study reported that infants who received supplemented formula scored higher on the MDI at 18 months than those who received standard formula. The other studies found no association between supplementation and any cognitive outcomes.

Seven reports on six observational studies investigating potential association of maternal or infant omega 3 fatty acid intake with childhood cognitive outcomes were identified. Several assessed infant cognitive development using the Bayley Scales of Infant Development (BSID), while others conducted follow up at seven, eight, and eleven years of age. In a model that controlled for 18 potential confounders, low levels of AA were associated with lower performance IQ and high levels of adrenic acid were associated with lower verbal IQ at age 8. Low levels of DHA were associated with lower verbal and full scale IQ. However, the authors caution that the effect sizes were small (approximately one-tenth of a standard deviation). The other studies reported no significant association between maternal or infant omega 3 intake and cognitive outcomes.

Randomized Controlled Trials

Interventions with pregnant women

The prior AHRQ-funded systematic review included one RCT on maternal supplementation during pregnancy; there were no differences between groups in the Fagan Test of Infant Intelligence at 6 and 9 months of age.

For the current systematic review, seven additional RCTs of pregnant women that reported cognitive outcomes were identified.^{34, 42, 64, 79-81, 142} All studies except one were conducted in Western countries; the exception was a study conducted in Bangladesh.⁸¹ Follow up times were diverse; children ranged in age from 14 days to 7 years. Due to the heterogeneity of

interventions, populations, outcome measures, and timing, meta-analysis was not conducted. Results are summarized below.

DHA Alone

In the US, Gustafson et al., 2013⁷⁹ randomized healthy pregnant women to capsules containing either vegetable oil or algal oil as a source of DHA (total of 0.600 g/d). The majority of enrollees were non-White (37.3% African American, 3.0% Asian, and 13.4% Hispanic). This study had a significantly lower rate of completion (78%) than other studies of pregnant women. Of 67 pregnant women enrolled, 52 completed the study through childbirth. Forty-one infants participated in the Neonatal Behavior Assessment at 14 days of age. Infants in the DHA group scored significantly higher on the autonomic and motor skills scales.

DHA plus EPA

Makrides, 2010³⁴ reported on the DOMInO trial conducted in Australia which randomized pregnant women to either capsules containing vegetable oil or fish oil (0.800 g DHA and 0.100 g/d EPA). The authors reported no difference in mean score on the cognitive component of the Bayley's Scale of Infant Development (BSID) Version III at 18 months of age.

Dunstan et al., 2008⁴² also conducted an RCT in Australia. Pregnant women with a history of allergy were randomized to olive oil capsule or fish oil capsule containing 2.2 g DHA and 1.1 g EPA. Children in the fish oil group scored significantly higher on the hand eye coordination component of the Griffith Mental Development Scale scores at 2.5 years of age. Differences were not statistically significant for the six other Griffith components.

Campoy et al., 2011¹⁴² reported on the NUHEAL study conducted in Germany, Spain, and Hungary. Pregnant women in the second half of pregnancy were randomized to three groups who all received a milk based supplement containing vitamins and minerals in amounts meeting the recommended intakes for European women. One of the groups received the supplement containing additional Omega 3 (DHA 0.500 g, EPA 0.100 g), while another received a supplement containing additional folic acid. Children were followed up at 6.5 years of age; differences in the Kauffman Assessment Battery for Children (K-ABC) were insignificant for all scales.

Tofail et al., 2006⁸¹ randomized pregnant women in Bangladesh to either soy oil capsules containing 0.27 g ALA and 2.25 g linoleic acid or fish oil capsules containing 1.2 g DHA and 1.8 g EPA. Only 151 of the 400 women enrolled (38%) completed the study. There were no significant differences in BSID II Mental Development Index (MDI) scores when infants were 10 months of age.

Helland et al., 2008⁸⁰ randomized pregnant women in Norway to 10 mL of either corn oil or cod liver oil (n-3 FA content not reported) from week 18 of pregnancy until 3 months after delivery. The effects on birth weight were described in the original report. At 7 years of age, no significant differences were observed in scores on the Kaufman Assessment Battery for Children (K-ABC) test.

DHA plus AA

Van Goor et al., 2011⁶⁴ reported on the Groningen LCPUFA study conducted in the Netherlands. One hundred and nineteen pregnant women were randomized to three groups who received soy oil capsules containing either no n-3 FA, DHA (0.220 g/d), or DHA (0.220 g) +AA (0.220 g). There were no differences between groups in the BSDI MDI at 18 months of age.

Postpartum Maternal Supplementation

Two RCTs and one prospective cohort study on maternal supplementation during breastfeeding were identified in the prior AHRQ systematic review. In these studies, supplementation with Omega-3 had no effect on cognition in offspring.

The current systematic review identified four new RCTs of lactating women that reported cognitive outcomes.^{55, 80, 113, 120} All were conducted in Western countries; most primarily enrolled white women. Sample sizes ranged from 89 to 545 women. Enrollment took place between 1995 and 2012. Follow up timing ranged from 9 months of age to 7 years. Due to heterogeneity of interventions, populations, outcome measures, and timing, meta-analysis was not conducted. Results are summarized below.

DHA plus EPA

Makrides et al., 2009¹¹³ reported on the DINO trial, conducted in Australia. Breast-feeding mothers of pre-term children were randomized to soy capsules or tuna oil capsules (0.500 g/d DHA) and instructed to take them daily until the infant reached "expected" date of delivery. When children were 18 months old, no difference was observed between groups in mean BSID MDI scores. However, for infants born weighing less than 1250g, the MDI in the high-DHA group was higher than with standard DHA in the unadjusted comparison (mean difference, 4.7; 95% CI, 0.2-9.2) but did not reach statistical significance following adjustment for gestational age, sex, maternal education, and birth order (mean difference, 3.8; 95% CI, -0.5 to 8.0).

Lauritzen et al., 2005⁵⁵ randomized pregnant Danish women with a fish intake below the population median (< 0.4 g n-3 LCPUFA·d⁻¹) and an intention to breastfeed for at least four months to muesli bars containing either olive oil or 4.5 g fish oil (DHA 60%). At one year of age, infants were assessed with the MacArthur Communicative Development Inventory Linguistic Development instrument. No significant differences were seen between groups.

In the U.S., Jensen et al., 2010¹²⁰ randomized breast feeding women to receive either vegetable oil capsule or high-DHA (0.200 g/d) algal triglyceride capsules for the first four months of lactation. At five years of age, children were assessed with the Wechsler Primary and Preschool Scale of Intelligence – Revised. No significant differences were observed between groups. The results for Helland et al., 2008,⁸⁰ which randomized pregnant and breastfeeding women to cod liver oil or vegetable oil, are described above in the section on pregnant women. This trial included supplementation during both pregnancy and lactation. No significant results were found for cognitive outcomes.

Infant Formula Supplementation with n-3 FA and Visual Acuity in Pre-term infants

The previous AHRQ systematic review identified six good quality RCTs in pre-term infants. Four of the five trials did not find an effect on cognition, as measured by the Bayley MDI score at various follow-up times. Two studies found a significant difference between the supplementation group and the placebo group on the Fagan Test of Infant Intelligence. Another RCT found no significant differences between groups in the Infant version of the MacArthur Communicative Development Inventories (MCDI).

Five RCTs identified for the current report (described in six publications) assessed the effects of supplementing pre-term infants with n-3 FA on cognitive outcomes.^{95, 103, 104, 113, 115, 126} Studies were conducted in Taiwan, the UK, Norway, Canada, and Australia. Follow up timing ranged

from 6 months to 10 years. Due to heterogeneity of interventions, populations, outcome measures, and timing, meta-analysis was not conducted. Results are summarized below.

DHA plus EPA

The DINO trial¹¹³ randomized breast-feeding mothers of pre-term children to soy capsules or tuna oil capsules; results are discussed in the section above on interventions with lactating women.

DHA plus AA

Fang et al., 2005¹²⁶ conducted an RCT in Taiwan that randomized preterm infants to either standard formula or formula supplemented with DHA (0.05%) and AA (0.10%) for 24 weeks. Infants were assessed at 6 months and 1 year of age using the BSID MDI. Infants who received supplemented formula scored significantly higher at both time points.

Both Henriksen et al., 2008¹⁰³ and Westerberg et al., 2011¹¹⁵ reported on a trial that randomized preterm infants in Norway to receive either soy oil drops (ALA 0.016 g/100 ml milk) or fish oil drops (DHA 0.032 g/100ml milk, AA 0.031 g/100 ml milk) during feeding. Mean duration of supplementation was 63 days. At six months of age, infants were assessed with the Ages and Stages instrument; no significant differences were found between treatment groups.¹⁰³ At 20 months of age, infants were re-assessed with the BSID MDI; the difference in scores between treatment groups was not statistically significant.¹¹⁵

DHA plus EPA plus AA

Clandinin et al., 2005¹⁰⁴ randomized preterm infants in Canada to either placebo formula, formula supplemented with algae oil ((DHA 0.017 g/100kcal (0.33% by weight), EPA 0.1% by weight, AA 0.034g/100kcal (0.67% by weight)) or formula supplemented with fish oil (DHA 0.017 g /100 kcal, AA 0.034g/100 kcal). A group of breast fed preterm infants served as another comparison group. Infants were assessed using the BSID II MDI at 118 weeksPMA. The groups supplemented with n-3 FA plus AA scored significantly higher than the non-supplemented groups.

Isaacs et al., 2011⁹⁵ randomized preterm infants in the UK to nine months of either standard formula or formula supplemented with DHA (0.5 g /100g fat), EPA (0.1 g/100g fat) and AA (0.04 g /100g fat). At 10 years of age, children were assessed with the Wechsler Abbreviated Scale of Intelligence, Weschler Individual Achievement Test, and the CMS Word Pairs instrument. Differences between groups were not statistically significant.

Infant Formula Supplementation with n-3 FA and Visual Acuity in Full Term infants

The original report identified 8 good-quality RCTs assessing the effect of supplementing term infants with n-3 FA on cognitive outcomes. Six of the eight studies found no significant difference between intervention and placebo groups in the Bayley's MDI score at any follow-up point. One study found a significantly higher score for the DHA+AA group compared with the control group at 18 months of age. A meta-analysis of 3 RCTs reporting the BSID MDI score at 12 months showed no difference between intervention and placebo groups.

The current review identified five reports on four RCTs of full term infants that measured cognitive outcomes.^{61, 65, 124, 133, 138} With the exception of a study conducted in Bangladesh, the studies were conducted in Western countries with primarily Caucasian samples. Follow-up

timing ranged from 10 months to 9 years. Due to heterogeneity of interventions, populations, outcome measures, and timing, meta-analysis was not conducted. Results are summarized below.

DHA Alone

Drover et al., 2011¹³⁸ followed up on children who had enrolled in the initial phase of the DIAMOND study at its Dallas, TX, site. Children had been randomized at birth to one year of standard cow's milk-based infant formula or formula containing 0.32%, 0.64%, or 0.96% DHA. At 18 months, children were assessed using the BSID II MDI. Differences among the four groups did not reach statistical significance; however, when all infants who received supplemented formula were grouped together, mean MDI score was significantly higher than the mean score of the group who received standard formula.

DHA plus AA

Birch et al., 2007¹³³ randomized healthy full term infants in the US to 17 weeks of either standard formula, formula supplemented with DHA (0.36%), or formula supplemented with DHA (0.36%) plus AA (0.72%). A breast fed group served as an additional comparison. At four years of age, the control and DHA-supplemented groups had significantly lower verbal IQ scores than the breast fed group (the group that received DHA plus AA had a non-significantly lower score than the breastfed group). However, no differences were observed between any of the formula-fed groups and the breast-fed group in performance IQ or full scale IQ.

DHA plus EPA

Meldrum et al., 2012¹²⁴ randomized healthy Australian full term infants to six months of either olive oil or fish oil (0.250 g/d DHA, 0.060 g/d EPA) supplements. At 18 months of age, infants were assessed using the cognitive component of the BSID-III: Differences between the groups were not significant.

Bouwstra et al., 2005⁶⁵ and de Jong et al., 2012⁶¹ reported on the Groningen LCPUFA study conducted in the Netherlands. Healthy infants were randomized to two months of standard formula or formula supplemented with DHA (0.30% by weight) plus AA (0.45% by weight). A breast fed group was included for comparison. At 18 months, no differences were observed in mean scores on the BSID MDI.⁶⁵ At nine years of age, according to IQ tests, no consistent beneficial effect of formula supplementation on cognitive development was found. Mean scores were not reported.⁶¹

Observational Studies

Seven reports on six observational studies investigating potential associations of maternal or infant omega 3 fatty acid intake with childhood cognitive outcomes were identified for the current report.^{117, 118, 127-129, 141, 143} All were conducted in the U.S. or Europe. Two studies collected diet information via food frequency questionnaires (FFQ) and five collected biomarker data. Several assessed infant cognitive development using the Bayley Scales of Infant Development (BSID), while others conducted follow up at seven, eight, and eleven years of age. Valent, et al.¹¹⁸ recruited pregnant women at 20 to 22 weeks gestation from a hospital in northern Italy. The primary purpose of the study was to assess the potential association between maternal mercury exposure and neurodevelopment outcomes in offspring. Information on maternal fish intake was collected by FFQ and levels of PUFAs were measured via maternal serum at week 32 of gestation. (Mercury levels were obtained from cord blood; it is unclear why PUFAs were not measured in the cord blood samples.) Of 900 women recruited, 767 (85%)

completed the study through childbirth. At 18 months, 632 children were assessed using the BSID III. Mothers of children lost to follow-up were of lower socio-economic status and had lower median IQ than those who participated. The authors developed a model that adjusted for maternal factors (concentration of mercury in hair during pregnancy, fish intake, weight gain during pregnancy, marital status, SES, number of children living at home, alcohol intake during pregnancy, breastfeeding history) and child factors (sex, birth weight, intake of fish, day care attendance) to assess whether concentration of ALA, EPA, DHA, LA, or ARA (mg/ml) were associated with BSID III scores. No statistically significant associations were found. However, child duration of fresh fish intake was associated with increased score on the cognitive component of the BSID III.

Keim, et al.¹⁴¹ analyzed data from the Pregnancy, Infection, and Nutrition Study. This prospective cohort study enrolled pregnant women from North Carolina hospitals; 1,169 were eligible for post-partum follow-up. At four months post-partum, the study analyzed n-3 FA content of mothers' breast milk samples and also collected data on n-3 FA content of any infant formula utilized. At 12 months of age, offspring cognition was assessed using the Mullen Scales of Early Learning. When controlling for infant sex, pre-term status, race/ethnicity, mother's education, and parity, no statistically significant associations between scores and AA, DHA, or total LCPUFA were identified.

Julvez et al.¹²⁸ and Guxens, et al.¹²⁷ reported on the INMA (Infancia Y Medio Ambiente) prospective cohort study conducted in Catalonia, Spain. Pregnant women (N = 657) were recruited from a public health center. Colostrum was collected two to four days after childbirth to measure LCPUFA content for a sub-sample of women (N = 277). Breastfeeding information was collected by questionnaire from all women when the offspring were 6 and 14 months of age. At 14 months of age, 504 infants were assessed using the BSID; in a model adjusted for child's age, maternal and paternal factors (education, social class, attachment to the child, IQ, mental health) and maternal smoking and alcohol use, PUFA levels in colostrum were not associated with scores. At four years of age, cognition was assessed in 434 children using the McCarthy Scales of Children's Abilities (MSCA). No association was seen between n-3 FA intake during infancy and MSCA scores¹²⁸ when adjusting for child (age, sex, day care attendance) and parental (age, parity, alcohol and smoking during pregnancy, education, social class, mental health, attachment with child) characteristics.

Bernard et al.¹¹⁷ reported on the EDEN prospective cohort study conducted in France. Using data on diet during last trimester of pregnancy collected via FFQ and a booklet displaying portion sizes, the researchers estimated intake of LA, AA, ALA, EPA, DHA, total n-6, total n-3, and total LCPUFAs for 1,585 women. At two years of age, 1,215 of their children were assessed using the Communicative Development Inventory (CDI). At three years of age 1,185 children were assessed using the Ages and Stages Questionnaire (ASQ), and Peg Moving Task Version 5. Among never breastfed children, a significant inverse relationship between maternal n6:n3 ratio and CDI and ASQ scores was reported. No significant associations were seen among scores of breastfed children and maternal intakes. Models were adjusted for child factors (gender, age, gestational age, firstborn, and main daytime caregiver) and parental factors (maternal age, obesity, energy intake, smoking and alcohol consumption during pregnancy, education, income, and maternal attachment).

Bakker, et al.¹²⁹ conducted a prospective cohort study that enrolled 750 pregnant women in the Netherlands. At childbirth, cord plasma was collected and analyzed for LCPUFA content. At 7 years of age, 306 children were assessed using the Kaufman Assessment Battery for Children

(K-ABC). Baseline characteristics of participating and non-participating children were not significantly different. Backward stepwise multiple linear regression analyses found no association between cord plasma AA or DHA and K-ABC scores.

Finally, Steer, et al.¹⁴³ analyzed data from the Avon Longitudinal Study Of Parents in Children, conducted in the UK. Blood samples from 5,222 pregnant women were analyzed for LCPUFA content. At 8 years of age, 2,839 of their children were assessed using the Wechsler Intelligence Scale for Children (WISC). In a model that controlled for 18 potential confounders, low levels of AA were associated with lower performance IQ, high levels of adrenic acid were associated with lower verbal IQ, and low levels of DHA were associated with lower verbal and full scale IQ scores. The authors caution that the effect sizes were small (approximately one-tenth of a standard deviation).

Table 17. RCTs for Cognitive development

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Birch et al., 2007¹³³</p> <p>Study name: Birch</p> <p>Study dates: 1993-1999</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up: 4 years 9412/11598</p> <p>Follow-up article(s) ^{136, 137}</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 79+40BF Infants completers 52+32BF</p> <p>Infant age: birth (0-5 days)</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: All participants were born at 37 to 40 weeks postmenstrual age. Only singleton births with birthweights appropriate for gestational age</p> <p>Exclusion Criteria: family history of milk-protein allergy, genetic or familial eye disease (e.g. hereditary retinal disease, strabismus), vegetarian or vegan maternal dietary patterns, maternal metabolic disease, anemia, or infection, presence of a congenital malformation or infection, jaundice, perinatal asphyxia, meconium aspiration, and any perinatal event which resulted in placement of the infant in the neonatal intensive care unit</p>	<p>Start time: Infants birth (0-5 days)</p> <p>Duration: Infants 17 weeks</p> <p>Arm 1: Control Description standard infant formula without added n-3 FA Brand name Enfamil with Iron Manufacturer Mead Johnson Nutritionals Active ingredients linoleic acid: 15% of total fats N-3 Composition. ALA 1.5% of total fats</p> <p>Arm 2: DHA Description infant formula fortified with DHA Brand name Enfamil with Iron, supplemented with DHASCO Manufacturer Formula: Mead Johnson; DHA: Martek Biosciences Active ingredients linoleic acid: 15% of total fats ALA 1.5% DHA 0.36%</p> <p>Arm 3: DHA+ARA Description infant formula fortified with DHA and ARA Brand name Enfamil with Iron, fortified with DHASCO and ARASCO Manufacturer Formula: Mead-Johnson; DHA, ARA: Martek Biosciences Active ingredients linoleic acid 15% ALA 1.5% DHA 0.36% AA 0.72%</p>	<p>Outcome Full Scale IQ Follow-up time 4 years Arm 1 Sample size 19 mean 101 SE (2.6) Arm 2 Sample size 16 mean 105.9 SE (3.9) Arm 3 Sample size 32 mean 107.5 SE (3.1)</p>
<p>Makrides et al., 2009¹¹³</p> <p>Study name: DINO</p> <p>Study dates: enrollment April 2001 to October 2005</p>	<p>Study Population: Preterm infants Breast-feeding women</p> <p>Pregnant enrolled 545</p> <p>Infants enrolled 657 Infants completers 614</p>	<p>Inclusion Criteria: infants born at < 33 wk of gestation</p> <p>Exclusion Criteria: Infants born with major congenital or chromosomal</p>	<p>Start time: Infants 4 days after birth</p> <p>Duration: Infants until infants reached their "expected" date of delivery</p> <p>Arm 1: Placebo Description Soy oil capsules or regular preterm formula</p>	<p>Outcome Bayley Mental Development Index Follow-up time 18 months Arm 1 Sample size 335 mean 93 SD (17.3) Arm 2 Sample size 322 mean 94.9 SD (14.5)</p>

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<p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations</p> <p>Follow-up: 18 months ¹¹¹, _{100 112 101 114}</p> <p>Follow-up article(s) ¹¹¹, _{112 100 101 114}</p>	<p>Lactating age: 30 years (5.5 years) NR</p> <p>Infant age: 4 days after birth (29 weeks gestation) 2 to 6 days after birth</p> <p>Race of Mother: White European (90%)</p>	<p>abnormalities, lactating women for whom tuna oil was contraindicated(women with bleeding disorders or taking anticoagulants)</p>	<p>Manufacturer Clover Corporation</p> <p>Dose six 500-mg soy oil capsules</p> <p>Blinding all capsules were similar in size, shape, and color</p> <p>Maternal conditions</p> <p>Infant conditions</p> <p>Current smoker 25.1% during pregnancy</p> <p>Pre-term birth 100%</p> <p>Low birth weight 44.5%</p> <p>Other conditions 1 SGA 18.6%</p> <p>Arm 2: tuna oil capsules</p> <p>Description DHA-rich tuna oil capsules or high-DHA formula</p> <p>Manufacturer Clover Corporation</p> <p>N-3 Compositiondesigned to achieve a breast milk DHA concentration that was approximately 1% of total fatty acids without altering the naturally occurring concentration of arachidonic acid (AA) in breast milk</p> <p>Dose 6 500 mg capsules</p> <p>Maternal conditions</p> <p>Infant conditions</p> <p>DHA Capsules: Intended to achieve breast milk concentration of 1.0%.Formula: 1.0%</p> <p>AA Capsules: not intended to alter AA levels. Formula: 0.6%</p> <p>Current smoker 25.6% during pregnancy</p>	
<p>Smithers et al., 2010¹¹¹</p> <p>Study name: DINO</p> <p>Study dates: April 2001 through September 2003</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product, Some authors</p>	<p>Study Population: Preterm infants</p> <p>Lactating enrolled 545</p> <p>Infants enrolled 657</p> <p>Infants completers 614</p> <p>Lactating enrolled 545</p> <p>Lactating age: 30 years (5.5 years) NR</p> <p>Infant age: 4 days after birth (29 weeks gestation) 2 to 6 days</p>	<p>Inclusion Criteria: infants born at < 33 wk of gestation</p> <p>Exclusion Criteria: Infants born with major congenital or chromosomal abnormalities or born to lactating women for whom tuna oil was contraindicated (women with bleeding disorders or taking anticoagulants)</p>	<p>Start time: Lactating 4 days after birth Infants 4 days after birth</p> <p>Duration: Lactating until infants reached their "expected" date of delivery. Infants until infants reached their "expected" date of delivery</p> <p>Arm 1: Placebo</p> <p>Description Soy oil capsules or standard preterm formula if not breastfeeding</p> <p>Manufacturer Clover Corporation</p> <p>N-3 Composition.</p> <p>Dose six 500-mg soy oil capsules</p> <p>Blinding all capsules were similar in size, shape, and color</p> <p>DHA Formula: 0.35%</p>	<p>Outcome MCDI vocabulary production score</p> <p>Follow-up time 26 months CA</p> <p>Arm 1 Sample size 67 mean 316 SD (192)</p> <p>Arm 2 Sample size 60 mean 308 SD (179)</p>

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<p>serve on scientific advisory boards for corporations</p> <p>Follow-up: 3 to 5 years^{100, 113},</p> <p>Follow-up article(s)^{112, 100, 113, 101, 114},</p>	<p>after birth</p> <p>Race of Mother: White European (90%)</p>		<p>AA Formula: 0.6%</p> <p>Total N-3 Capsules: did not change FA content of breastmilk</p> <p>Arm 2: DHA</p> <p>Description DHA-rich tuna oil capsules or high-DHA formula</p> <p>Manufacturer Clover Corporation</p> <p>N-3 Composition DHA-rich tuna oil capsules to achieve a breast milk DHA concentration that was approximately 1% of total fatty acids without altering the naturally occurring concentration of arachidonic acid (AA) in breast milk</p> <p>Dose six 500 mg capsules per day</p> <p>DHA Capsules: Achieved breast milk concentration of 1.0%. Formula: 1.0%</p> <p>AA Capsules: Did not change AA in breastmilk.</p> <p>Formula 0.6%</p>	
<p>Makrides et al., 2010³⁴</p> <p>Study name: DOMInO</p> <p>Study dates: 2005-2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up article(s)^{48, 49, 50, 51, 52, 53, 3},</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 2399 Pregnant withdrawals 1</p> <p>Infants enrolled 605 Infants withdrawals 32 Infants completers 726</p> <p>Pregnant age: 28.9 (DHA5.7; control5.6)</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: with singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments</p> <p>Exclusion Criteria: already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the</p>	<p>Start time: Pregnant < 21 week's gestation</p> <p>Duration: NR</p> <p>Arm 1: vegetable oil capsules</p> <p>Description a blend of 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions</p> <p>Manufacturer Efamol, Surrey, England.</p> <p>Dose 3* 500mg capsule / day</p> <p>Blinding All capsules were similar in size, shape, and color</p> <p>Arm 2: DHA</p> <p>Description DHA-rich fish oil concentrate</p> <p>Manufacturer ; Incromega 500 TG, Croda Chemicals, East Yorkshire, England</p> <p>Dose 500mg capsule *3/day</p> <p>DHA 800mg</p> <p>EPA 100mg</p>	<p>Outcome BSID III (cognitive component)</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 375 weighted mean 101.75 SD (12.56)</p> <p>Arm 2 Sample size 351 weighted mean 101.81 SD (11.05)</p>

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		main language spoken at home		
<p>Lauritzen et al., 2005⁵⁵</p> <p>Study name: Danish National Birth Cohort</p> <p>Study dates: enrolled in 1999</p> <p>Study design: Trial randomized parallel</p> <p>Location: Denmark</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: reports 9 months, 1 year, 2 years 6643?</p> <p>Follow-up article(s) ^{44, 54}</p>	<p>Study Population: Healthy infants Breast-feeding women</p> <p>Lactating enrolled 122 Lactating completers 89</p> <p>Infants enrolled 122 Infants completers 89</p> <p>Lactating enrolled 122 Lactating completers 89</p> <p>Pregnant age: NR (NR) NR</p> <p>Infant age: 9 days (3 days) NA</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: pregnant women with a fish intake below the population median (< 0.4 g n-3 LCPUFA·d⁻¹), uncomplicated pregnancy, a normal prepregnancy body mass index (< 30 kg·m⁻²), no metabolic disorders, an intention to breastfeed for at least four months. Newborns had to be healthy, singleton, term infants with normal weight for gestation [33] and an Apgar score > 7 five minutes after delivery.</p> <p>Exclusion Criteria: NR</p>	<p>Start time: Lactating 9 days after birth Infants 9 days after birth</p> <p>Duration: Lactating 4 months Infants 4 months</p> <p>Arm 1: placebo group Description olive oil in musli bars, cookies, or capsules Manufacturer BASF Dose one bar/cookie/capsule containing 4.5 g olive oil Blinding identical bars/cookies/capsules Arm 2: fish oil Description fish oil in musli bars, cookies, or capsules Manufacturer BASF N-3 Composition 1.5 g of n-3 LCPUFA Dose one bar/cookie/capsule containing 4.5 g fish oil DHA 0.9 g Total N-3 Other FA (not DHA): 0.6 g Arm 3: high n-3 reference group Description top quartile fish intake at baseline N-3 Composition > 0.8 n-3 LCPUFA/d Dose no supplementation, high fish intake</p>	<p>Outcome MacArthur Communicative Development Inventory Linguistic Development: late gestures Follow-up time 1 year Arm 1 Sample size 37 mean 15 SD (7) Arm 2 Sample size 52 mean 14 SD (6) Arm 3 Sample size 42 mean 16 SD (7) Outcome MacArthur Communicative Development Inventory Linguistic Development: number of irregular words Follow-up time 2 years Arm 1 Sample size 31 median 3 IQR (1,7) Arm 2 30/40 (75%) Arm 3 Sample size 40 median 4 IQR (2,5) Outcome MacArthur Communicative Development Inventory Linguistic Development: number of over regularized words Follow-up time 2 years Arm 1 Sample size 31 median 1 IQR (0,3) Arm 2 10/40 (25%) Arm 3 Sample size 40 median 1 IQR (0,3) Outcome MacArthur Communicative Development Inventory Linguistic Development: early gestures Follow-up time 1 year Arm 1 Sample size 37 median 11 IQR (9, 12) Arm 2 Sample size 52 median 11 IQR (8, 12) Arm 3 Sample size 42 median 12 IQR (10, 13) Outcome MacArthur Communicative Development Inventory Linguistic Development: percent starting to talk Follow-up time 1 year Arm 1 6/37 (16%) Arm 2 6/52 (12%) Arm 3 7/42 (17%) Outcome MacArthur Communicative Development Inventory Linguistic</p>

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				<p>Development: phrases understood Follow-up time 1 year Arm 1 Sample size 37 mean 11 SD (6) Arm 2 Sample size 52 mean 11 SD (5) Arm 3 Sample size 42 mean 11 SD (5) Outcome MacArthur Communicative Development Inventory Linguistic Development: talk about abstract Follow-up time 2 years Arm 1 29/31 (94%) Arm 2 Sample size 40 median 1 IQR (0,6) Arm 3 38/40 (95%) Outcome MacArthur Communicative Development Inventory Linguistic Development: use grammar Follow-up time 2 years Arm 1 10/31 (32%) Arm 2 Sample size 40 mean 242 SD (170) Arm 3 16/40 (40%) Outcome MacArthur Communicative Development Inventory Linguistic Development: vocabulary comprehension Follow-up time 1 year Arm 1 Sample size 37 mean 71 SD (45) Arm 2 Sample size 52 mean 54 SD (37) Arm 3 Sample size 42 mean 65 SD (40) Outcome MacArthur Communicative Development Inventory Linguistic Development: vocabulary production Follow-up time 1 year Arm 1 Sample size 37 median 5 IQR (2, 11) Arm 2 Sample size 52 median 3 IQR (1,9) Arm 3 Sample size 42 median 5 IQR (1,11) Follow-up time 2 years Arm 1 Sample size 31 mean 297 SD (147) Arm 2 Sample size 40 mean 3.3 SD (170) Arm 3 Sample size 40 mean 312 SD (146) Outcome problem solving Follow-up time 9 months Arm 1 Sample size 38 mean 4.3 SD (3.6) Arm 2 Sample size 48 mean 4.5 SD (3.1) Arm 3 Sample size 42 mean 4.5 SD (3.3)</p>

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<p>Drover et al., 2011¹³⁸</p> <p>Study name: Diamond</p> <p>Study dates: 2003-2006</p> <p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 18 months¹³²</p> <p>Follow-up article(s)^{132, 139}</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 181 Infants withdrawals 64 Infants completers 117</p> <p>Infant age: 18.1 month (0.2)</p> <p>Race of Mother: White European (70%) Minority (30%)</p>	<p>Inclusion Criteria: Children who had enrolled in the initial phase of the DIAMOND study at the Dallas site, and had completed the 12-month feeding protocol and the 12-month primary outcome visit (141 children)</p> <p>Exclusion Criteria: Infants who had diseases or congenital abnormalities known to affect growth, development, visual or cognitive maturation, or who had poor formula intake did not participate in the study. Infants were also excluded if they had received human milk within 24 h of randomization, or if they were born to mothers with chronic illness such as HIV disease, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or substance abuse</p>	<p>Start time: Infants birth (1 9 days)</p> <p>Duration: Infants 1 year</p> <p>Arm 1: No DHA (Control) Description Cow's milk-based infant formula without DHA or ARA Brand name Enfamil® with iron Manufacturer Mead Johnson & Co, Evansville, IN Blinding After obtaining signed assent from a parent, the study coordinator opened the next sequentially-numbered opaque sealed envelope to determine the code of the study formula to be assigned to that infant. All recruiting personnel, parents or guardians, study monitors, researchers, and pediatricians were masked to the infant's assigned formula.</p> <p>Arm 2: 0.32% DHA Description 0.32% fatty acids from DHA & 0.64% ARA Brand name Enfamil LIPIL® Manufacturer Enfamil LIPIL® DHA 17mg/100 kcal, 0.32% DHA with 0.32% fatty acids from DHA AA 34mg/100 kcal, 0.64% ARA</p> <p>Arm 3: 0.64% DHA Description 0.64% DHA & 0.64% ARA Brand name Enfamil LIPIL Manufacturer Mead Johnson Nutrition DHA 34 mg/100 kcal AA 34mg/100 kcal, 0.64% ARA</p> <p>Arm 4: 0.96% DHA Description 0.96% DHA & 0.64% ARA Brand name Enfamil LIPIL Manufacturer Mead Johnson Nutrition DHA 54 mg/100 kcal; 0.96% DHA AA 34 mg/100 kcal; 0.64% ARA</p>	<p>Outcome BSID II - MDI Follow-up time 18 months Arm 1 Sample size 28 mean 98.4 SD (13.1) Arm 2 Sample size 29 mean 105.2 SD (10.7) Arm 3 Sample size 32 mean 104.2 SD (9.8) Arm 4 Sample size 28 mean 102.6 SD (11.9)</p>
<p>Drover et al., 2012¹³⁹</p> <p>Study name: Diamond</p> <p>Study dates: NR</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 343 Infants completers 88</p>	<p>Inclusion Criteria: Healthy term singleton-birth infants born in any of 5 hospitals</p> <p>Exclusion Criteria:</p>	<p>Start time: Infants <=9 days after birth</p> <p>Duration: Infants 12 months</p> <p>Arm 1: Control group Description Standard infant formula</p>	<p>Outcome School Readiness Composite (SRC) Follow-up time 2.5 years Arm 1 Sample size 19 mean 9.79 SD (2.42) Arm 2 Sample size 23 mean 10.3 SD</p>

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<p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 3.5 years ^{138, 132}</p> <p>Follow-up article(s) ^{138, 132}</p>	<p>Pregnant age: 31 years (4 years)</p> <p>Infant age: <= 9 days 1 to 9 days</p> <p>Race of Mother: NR (100)</p>	<p>Infants who had diseases or congenital abnormalities known to affect growth, development, visual or cognitive maturation, Infants were also excluded if they had received human milk within 24 h of randomization, or if they were born to mothers with chronic illness such as HIV disease, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or substance abuse</p>	<p>Brand name Enfamil with Iron Manufacturer Mead-Johnson Nutrition, Evansville IN Arm 2: 0.32% DHA formula Brand name Enfamil LIPIL® Manufacturer Mead-Johnson; DHA and ARA from algal and fungal oils manufactured by Martek Biosciences N-3 Composition 17mg DHA/100kcal DHA 0.32% or 17mg/100kcal AA 0.64% FA or 34mg/100kcal Arm 3: 0.64% DHA formula Brand name NR Manufacturer NR DHA 34mg/100kg AA 0.64% FA or 34mg/100kcal Arm 4: 0.96% DHA formula Brand name NR Manufacturer NR DHA 51mg/100kg AA 0.64% FA or 34mg/100kcal</p>	<p>(1.92) Arm 3 Sample size 27 mean 10.63 SD (2.75) Arm 4 Sample size 24 mean 10.79 SD (2.62)</p>
<p>Dunstan et al., 2008⁴²</p> <p>Study name: Dunstan</p> <p>Study dates: 2000-2003</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: NR</p> <p>Follow-up article(s) ^{56, 57, 58, 59}</p>	<p>Study Population: Healthy infants Pregnant women with allergies</p> <p>Pregnant enrolled 98 Pregnant completers 83</p> <p>Infants enrolled 83 Infants withdrawals 11 (7 FO, 4 control) Infants completers 72</p> <p>Pregnant age: Fish oil: 30.9 Control: 32.6 (Fish oil: 3.7 Control: 3.6)</p> <p>Infant age: Term (mean gestational period 275 days)</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: Healthy term infants of pregnant women enrolled in RCT of gestational supplementation</p> <p>Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune</p>	<p>Start time: Pregnant 20 weeks gestation</p> <p>Duration: Pregnant to term</p> <p>Arm 1: Control Description olive oil placebo Blinding capsules image matched Maternal conditions Current smoker 0% Maternal allergies 100% Arm 2: Fish oil Description same Manufacturer Ocean Nutrition, Halifax Nova Scotia Active ingredients 3-4mg/g vitamin E Viability none reported Dose 4 1-gm capsules fish oil per day Maternal conditions DHA 2.2 EPA 1.1 Current smoker 0% Maternal allergies 100% Other comment 1 fish oil supplying 2,2g/d DHA and</p>	<p>Outcome Griffith Mental Development Scales: Eye and hand coordination Follow-up time 2.5 years Arm 1 Sample size 39 mean 108 SD (11.3) Arm 2 Sample size 33 mean 114 SD (10.2) Outcome Griffith Mental Development Scales: Performance Follow-up time 2.5 years Arm 1 Sample size 39 mean 115.8 SD (13.7) Arm 2 Sample size 33 mean 120.9 SD (12.7) Outcome Griffith Mental Development Scales: Practical reasoning Follow-up time 2.5 years Arm 1 Sample size 39 mean 113.6 SD (15) Arm 2 Sample size 33 mean 114.3 SD (14.5) Outcome Griffith Mental Development Scales: Speech and hearing Follow-up time 2.5 years Arm 1 Sample size 39 mean 109.6 SD (14.9)</p>

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		response) or if cord blood was not collected	1.1g/day EPA	<p>Arm 2 Sample size 33 mean 112 SD (15) Outcome Griffith Mental Development Scales: General quotient score Follow-up time 2.5 years Arm 1 Sample size 39 mean 110.5 SD (10.6) Arm 2 Sample size 33 mean 114.2 SD (9.8) Outcome Griffith Mental Development Scales: Personal social Follow-up time 2.5 years Arm 1 Sample size 39 mean 109.4 SD (11.5) Arm 2 Sample size 33 mean 112.4 SD (11.9) Outcome Griffith Mental Development Scales: Locomotor Follow-up time 2.5 years Arm 1 Sample size 39 mean 107.9 SD (12.6) Arm 2 Sample size 33 mean 112.5 SD (12.2)</p>
<p>Bouwstra et al., 2005⁶⁵</p> <p>Study name: Groningen LCPUFA study</p> <p>Study dates: 1997-2002</p> <p>Study design: Trial randomized parallel</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 18 months ⁶⁶, ⁶²</p> <p>Follow-up article(s) ⁶¹, ⁶², ⁶³, ⁶⁴, ⁶⁶, ⁶⁷, ⁶⁸, ³⁵</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 472 Infants completers 446</p> <p>Mother age: 31 years (5 years) NR</p> <p>Infant age: birth</p> <p>Race of Mother: White European (100%)</p>	<p>Inclusion Criteria: healthy term infants</p> <p>Exclusion Criteria: infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.</p>	<p>Start time: Infants Birth</p> <p>Duration: Infants 2 months</p> <p>Arm 1: Control group Description Standard formula Brand name Nutrilon premium Manufacturer Zoetermeer, Netherlands Active ingredients linoleic acid (11mol%); ALA 1.27 mol% Dose ad lib Maternal conditions Current smoker 31% during pregnancy Maternal abuse of alcohol/psychotropic drugs Alcohol USE during pregnancy 8% Arm 2: LCPUFA formula Description LCPUFA formula Dose ad lib Maternal conditions DHA 0.30% DHA AA 0.45% AA</p>	<p>Outcome Bayley Scales of Infant Development (Mental Development Index) Follow-up time 18 months Arm 1 Sample size 155 mean 105.4 SD (15) Arm 2 Sample size 135 mean 102.7 SD (15.4)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Current smoker 31% during pregnancy Maternal abuse of alcohol/psychotropic drugs 9% used alcohol during pregnancy Arm 3: breast feeding group Description breast fed, no formula Maternal conditions Current smoker 19% smoked during pregnancy Maternal abuse of alcohol/psychotropic drugs 24% used alcohol during pregnancy	
<p>Goor et al., 2011⁶⁴</p> <p>Study name: Groningen LCPUFA study</p> <p>Study dates: 2004-2009</p> <p>Study design: Trial randomized parallel</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 18 months (multiple IDs)</p> <p>Follow-up article(s) ^{61, 62, 63, 65, 66, 67, 68, 35}</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 119</p> <p>Infants enrolled 119</p> <p>Infants completers 114</p> <p>Pregnant age: Placebo: 32.7 DHA: 32.5 DHA+AA: 32.9 (Placebo: 5.1 DHA: 4.4 DHA+AA: 4.8)</p> <p>Infant age: 18 months</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: women with a first or second low-risk singleton pregnancy, between the 14th and 20th weeks of pregnancy</p> <p>Exclusion Criteria: women with vegetarian or vegan diets; women with diabetes mellitus; birth complications</p>	<p>Start time: Pregnant 14th-20th week pregnancy Lactating 3 months after delivery Mothers 3 months after delivery Infants NR</p> <p>Duration: Pregnant NR Lactating 33-39 weeks Mothers 33-39 weeks Infants NR</p> <p>Arm 1: placebo Description Soy bean oil Brand name none</p> <p>Arm 2: DHA Description DHA plus soy bean oil Brand name Marinol D40 Manufacturer Lipid Nutrition B.V., Wormerveer, The Netherlands; AA: Dose 1 capsule DHA and 1 capsule soy bean oil once a day ALA 32 mg/d DHA 220 mg/d EPA 34 mg/d</p> <p>Arm 3: DHA+AA Description DHA plus AA Brand name AA: no brand name Manufacturer Wuhan Alking Bioengineering Co. Ltd., Wuhan, China Dose 2 capsules once a day ALA 7 mg/d DHA 220 mg/d EPA 36 mg/d AA 220 mg per capsule</p>	<p>Outcome Bayley Scale of Infant Development (Mental developmental index)</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 34 mean 115.2 SD (11.6)</p> <p>Arm 2 Sample size 41 mean 113.7 SD (13)</p>
<p>de Jong et al., 2012⁶¹</p> <p>Study name: Groningen</p>	<p>Study Population: Healthy infants</p>	<p>Inclusion Criteria: healthy infants</p>	<p>Start time: Infants birth</p> <p>Duration: Infants 2 months</p>	<p>No usable data.</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>LCPUFA study</p> <p>Study dates: Enrollment from February 1997 through October 1999, follow-up 9 years later</p> <p>Study design: Trial randomized parallel</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: 9 years ^{66, 65, 62}</p> <p>Follow-up article(s) ^{62, 63, 64, 65, 66, 67, 68, 35}</p>	<p>Infants enrolled 314 Infants completers 214</p> <p>Mother age: 31 years (5 years) NR</p> <p>Infant age: birth (NA) NA</p> <p>Race of Mother: White European (100%)</p>	<p>Exclusion Criteria: infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.</p>	<p>Arm 1: Control formula Description Standard formula with no supplemental LCPUFA Brand name Nutrilon premium Manufacturer Nutricia, Zoetermeer, Netherlands Active ingredients linoleic acid (11mol%); ALA 1.27 mol% Blinding NR Maternal conditions Current smoker 23% during pregnancy Other maternal conditions 1arm_1_maternal_conditions_other1 Other maternal conditions 2 maternal hypertension 17%</p> <p>Arm 2: Omega 3 supplemented formula Description LCPUFA formula Manufacturer Nutricia, Zoetermeer, Netherlands Active ingredients linoleic acid (11mol%); ALA 1.30 mol% Maternal conditions DHA 0.30% by weight AA 0.45% by weight Current smoker 32% during pregnancy Other maternal conditions 1arm_2_maternal_conditions_other1 Other maternal conditions 2 maternal hypertension 12%</p> <p>Arm 3: breastfeeding comparison group Maternal conditions Current smoker 10% during pregnancy Other maternal conditions 1arm_3_maternal_conditions_other1 Other maternal conditions 2 maternal hypertension 9%</p>	
<p>Meldrum et al., 2012¹²⁴</p> <p>Study name: Infant FishOil Supplementation Study (IFOS)</p> <p>Study dates: recruitment from June 2005 through</p>	<p>Study Population: Pregnant women with allergies</p> <p>Pregnant enrolled 420</p> <p>Infants enrolled 420 Infants completers 287</p>	<p>Inclusion Criteria: allergic pregnant women were recruited as their infants are at a higher risk of developing allergic disease. Maternal atopy was defined by at least one positive skin prick</p>	<p>Start time: Infants birth</p> <p>Duration: Infants 6 months</p> <p>Arm 1: placebo Description olive oil capsule Manufacturer Ocean Nutrition, Canada Active ingredients 66.6 % n-9 oleic acid</p>	<p>Outcome Bayley Scales of Infant and Toddler Development (BSID-III) Composite Scores Cognitive Follow-up time 18 months Arm 1 Sample size 149 mean 105.28 SD (19.9) Arm 2 Sample size 138 mean 107.65 SD (11.6)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>October 2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, None, Manufacturer supplied product</p> <p>Follow-up article(s) Protocol ^{144, 125}</p>	<p>Mother age: NR (NR) NR</p> <p>Infant age: Birth (NA) NA</p> <p>Race of Mother: NR</p>	<p>test to at least one of a defined panel of allergens.</p> <p>Exclusion Criteria: maternal smoking, a pre-existing medical condition or high-risk pregnancy, more than three fish meals consumed per week or fish oil intake during pregnancy in excess of 1000 mg/d, preterm delivery, and infants with significant congenital abnormalities or medical conditions.</p>	<p>Viability he composition was regularly tested by an independent laboratory during the trial</p> <p>Dose one 650 mg capsule</p> <p>Blinding image and scent matched</p> <p>Arm 2: fish oil capsul</p> <p>Manufacturer Ocean Nutrition, Canada</p> <p>Viability he composition was regularly tested by an independent laboratory during the trial.</p> <p>Dose one 650 mg capsule</p> <p>DHA 280 mg</p> <p>EPA 110 mg</p>	<p>Outcome Bayley Scales of Infant and Toddler Development (BSID-III) Standard Scores Cognitive</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 149 mean 11.43 SD (2.3)</p> <p>Arm 2 Sample size 138 mean 11.55 SD (2.2)</p> <p>Outcome Macarthur-Bates Communicative Development Inventory raw score: early gestures</p> <p>Follow-up time 12 months</p> <p>Arm 1 Sample size 66 mean 9.56 SD (3.14)</p> <p>Arm 2 Sample size 62 mean 10.29 SD (3.5)</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 84 mean 13.62 SD (7.7)</p> <p>Arm 2 Sample size 77 mean 14.09 SD (2.3)</p> <p>Outcome Macarthur-Bates Communicative Development Inventory raw score: later gestures</p> <p>Follow-up time 12 months</p> <p>Arm 1 Sample size 66 mean 11.26 SD (7.5)</p> <p>Arm 2 Sample size 62 mean 15.16 SD (8.3)</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 84 mean 28.08 SD (7.7)</p> <p>Arm 2 Sample size 77 mean 30.81 SD (7.6)</p> <p>Outcome Macarthur-Bates Communicative Development Inventory raw score: phrases understood</p> <p>Follow-up time 12 months</p> <p>Arm 1 Sample size 66 mean 13.6 SD (5.8)</p> <p>Arm 2 Sample size 62 mean 13.34 SD (6.7)</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 84 mean 23.5 SD (5.1)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				<p>Arm 2 Sample size 77 mean 24.06 SD (4.7)</p> <p>Outcome Macarthur-Bates Communicative Development Inventory raw score: total gestures</p> <p>Follow-up time 12 months</p> <p>Arm 1 Sample size 66 mean 20.76 SD (10.1)</p> <p>Arm 2 Sample size 62 mean 25.47 SD (10.9)</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 84 mean 41.48 SD (9.3)</p> <p>Arm 2 Sample size 77 mean 44.75 SD (9)</p> <p>Outcome Macarthur-Bates Communicative Development Inventory raw score: words spoken</p> <p>Follow-up time 12 months</p> <p>Arm 1 Sample size 66 mean 5.52 SD (8.7)</p> <p>Arm 2 Sample size 62 mean 6.11 SD (7.5)</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 84 mean 58.5 SD (63.5)</p> <p>Arm 2 Sample size 77 mean 49.16 SD (55.8)</p> <p>Outcome Macarthur-Bates Communicative Development Inventory raw score: words understood</p> <p>Follow-up time 12 months</p> <p>Arm 1 Sample size 66 mean 61.42 SD (52.2)</p> <p>Arm 2 Sample size 62 mean 68.3 SD (47.6)</p> <p>Follow-up time 18 months</p> <p>Arm 1 Sample size 84 mean 190.43 SD (94.5)</p> <p>Arm 2 Sample size 77 mean 199.09 SD (83.7)</p>
<p>Clandinin et al., 2005¹⁰⁴</p> <p>Study name: NR</p> <p>Study dates: NR</p>	<p>Study Population: Preterm infants</p> <p>Infants enrolled 361 preterm+105 term</p>	<p>Inclusion Criteria: Phase I: gestational age <35 weeks PMA and received <10 total days of enteral feedings of</p>	<p>Start time: Infants 10 days of age</p> <p>Duration: Infants 118 weeks</p> <p>Arm 1: Control</p>	<p>Outcome BSID II MDI</p> <p>Follow-up time 118 weeks</p> <p>Arm 1 Sample size 54 mean 77 SE (2)</p> <p>Arm 2 Sample size 44 mean 83 SE (2)</p> <p>Arm 3 Sample size 60 mean 87 SE (2)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study design: Trial randomized parallel</p> <p>Location: Canada</p> <p>Funding source / conflict: Industry</p>	<p>breastfed Infants completers 179 preterm and 76/105 term breastfed</p> <p>Infant age: 30.6 weeks postmenstrual age 24-36 weeks postmenstrual age</p> <p>Race of Mother: NR (100)</p>	<p>>30 mL/kg per day. Infants initially fed human milk were not enrolled unless formula was started within 10 days after completing the first day of human milk feeding Phase II: completion of phase I and $\geq 80\%$ enteral intake from study formula during hospitalization and 100% of caloric intake from study formula at completion of phase 1. Birth weight <1500g</p> <p>Exclusion Criteria: congenital abnormalities of the gastrointestinal tract, hepatitis, hepatic or biliary pathology, necrotizing enterocolitis confirmed before enrollment, or history of underlying disease or congenital malformation likely to interfere with evaluation</p>	<p>Description Non-supplemented premature, discharge, and term formula</p> <p>Dose Ad lib</p> <p>Blinding Not reported</p> <p>Infant conditions</p> <p>Pre-term birth 119 (100%)</p> <p>Arm 2: Algal-DHA</p> <p>Description supplemented premature infant formula supplemented with DHA from algal oil</p> <p>Manufacturer Martek Biosciences</p> <p>Dose ad lib</p> <p>DHA 17mg/100kcal (0.33% by weight)</p> <p>EPA 0.1% by weight</p> <p>AA 34mg/100kcal (0.67% by weight)</p> <p>Arm 3: Fish-DHA</p> <p>Description Premature infant formula supplemented with DHA from tuna fish oil</p> <p>Manufacturer Martek Biosciences</p> <p>Dose ad lib</p> <p>DHA 17mg DHA/100 kcal</p> <p>AA 34mg/100 kcal</p> <p>Arm 4: Reference</p> <p>Description Breast fed term infants</p>	<p>Arm 4 Sample size 58 mean 98 SE (2)</p>
<p>Fang et al., 2005¹²⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Trial randomized parallel</p> <p>Location: Taiwan</p> <p>Funding source / conflict: Manufacturer supplied</p>	<p>Study Population: Preterm infants</p> <p>Infants enrolled 28</p> <p>Infants withdrawals 1</p> <p>Infants completers 27</p> <p>Infant age: 1 week (mean gestation age 33 weeks) (0.5 week) NA</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: (1) A gestational age at birth between 30 and 37 weeks; (2) Normal fundus oculi; (3) Recruitment prior to commencement of feeding</p> <p>Exclusion Criteria: (1) Breast feeding; (2) A maternal history of infection, diabetes mellitus, gestational</p>	<p>Start time: Infants 1 week after birth</p> <p>Duration: Infants 24 weeks</p> <p>Arm 1: placebo</p> <p>Description infant formula based on the composition of human milk</p> <p>Brand name Neoangelac</p> <p>Manufacturer Multipower Enterprise Corporation</p> <p>N-3 Composition.</p> <p>Dose Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months</p> <p>N-6 N-3 10:1 linoleic:linolenic</p>	<p>Outcome Mental Development Index</p> <p>Follow-up time 1 year</p> <p>Arm 1 Sample size 11 mean 90.5 SD (6.9)</p> <p>Arm 2 Sample size 16 mean 98.7 SD (8)</p> <p>Follow-up time 6 months</p> <p>Arm 1 Sample size 11 mean 91.7 SD (10.4)</p> <p>Arm 2 Sample size 16 mean 96.1 SD (8.6)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
product		diabetes mellitus, cocaine or alcohol abuse, systemic diseases or if intrauterine growth retardation had been diagnosed during pregnancy; (3) Major congenital abnormality; (4) Severe intraventricular hemorrhage > grade 2; (5) Cystic periventricular leukomalacia; (6) Retinopathy of prematurity stage 2; (7) Bronchopulmonary dysplasia on radiographs or oxygen usage 28 days; (8) Body weight less than the third percentile; (9) Surgical intervention for necrotizing enterocolitis (10) Mechanical ventilation after achieving enteral intake > 110 kcal/kg per day; (11) A 5-min Apgar score < 7; (12) Administration of blood transfusion, blood products, or parenteral lipids with DHA or AA.	Arm 2: Neoangelac Plus Description Neoangelac supplemented with Omega 3 Brand name Neoangelac Plus Manufacturer Multipower Enterprise Corporation Dose Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months DHA 0.05% AA 0.10%	
Gustafson et al., 2013 ⁷⁹ Study name: NR Study dates: may 2009 - july 2011 Study design: Trial randomized parallel	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 67 Pregnant withdrawals 12 Pregnant completers 52 Infants enrolled 44 Infants completers 41	Inclusion Criteria: between 16–35.9 years of age and carrying a singleton pregnancy between the 12th and 20th week of gestation Exclusion Criteria: any serious health condition likely to affect the growth	Start time: Pregnant 12-20 week gestation Infants birth Duration: Pregnant till birth Arm 1: Placebo Description g 50% soy and 50% corn oil Manufacturer Martek Biosciences, now DSM Nutritional Products Dose 3 capsule a day each 500 mg	Outcome Neonatal Behavior Assessment: state organization Follow-up time 1-14 days post-partum Arm 1 Sample size 12 mean 13.5 SD (13.89) Arm 2 Sample size 15 mean 15.13 SD (8.02) Outcome Neonatal Behavior Assessment: autonomic Follow-up time 1-14 days post-partum

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Location: US</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p>	<p>Pregnant age: placebo 25.6+; DHA 25.5 (placebo 4.8; DHA 4.3)</p> <p>Race of Mother: White European (46.3) Black (37.3) Asian (3) Hispanic (13.4)</p>	<p>and development of the fetus or health of the mother including cancer, lupus, hepatitis, diabetes mellitus (Type1, Type 2 or gestational) or HIV/AIDS at baseline or fetal cardiac structural or conduction defects.</p> <p>Women who self-reported illicit drug use or alcohol use during pregnancy and those with hypertension or BMI ≥40 were excluded.</p> <p>Women who were taking more than 200 mg/day DHA in prenatal vitamins or over the counter supplements were excluded from participation</p>	<p>Blinding Only members of the investigational pharmacy knew the subject allocation. Participants and all members of the investigational team were blinded to the intervention assignment. Participants were allocated to either group based on the simple randomization procedure using random numbers generated by SAS. All capsules were the same color, size, weight and the oils were orange-flavored to prevent investigator or subject bias.</p> <p>Arm 2: algal oil as a source of DHA (200 mg of DHA per capsule for a total of 600 mg DHA/day)</p> <p>Dose 3 capsule of 200mg DHA total 600 mg DHA 200 mg * 3</p>	<p>Arm 1 Sample size 12 mean 14.83 SD (16.9)</p> <p>Arm 2 Sample size 15 mean 18.13 SD (14.48)</p> <p>Outcome Neonatal Behavior Assessment: motor</p> <p>Follow-up time 1-14 days post-partum</p> <p>Arm 1 Sample size 12 mean 23.08 SD (11.4)</p> <p>Arm 2 Sample size 15 mean 26.07 SD (18.13)</p> <p>Outcome Neonatal Behavior Assessment: reflexes</p> <p>Follow-up time 1-14 days post-partum</p> <p>Arm 1 Sample size 12 mean 21.92 SD (14.45)</p> <p>Arm 2 Sample size 15 mean 22.6 SD (14.33)</p> <p>Outcome Neonatal Behavior Assessment: state regulation</p> <p>Follow-up time 1-14 days post-partum</p> <p>Arm 1 Sample size 12 mean 16.42 SD (20.02)</p> <p>Arm 2 Sample size 15 mean 16.93 SD (20.06)</p> <p>Outcome Neonatal Behavior Assessment: habituation</p> <p>Follow-up time 1-14 days post-partum</p> <p>Arm 1 Sample size 12 mean 9.92 SD (9.28)</p> <p>Arm 2 Sample size 15 mean 8.47 SD (9.26)</p> <p>Outcome Neonatal Behavior Assessment: orienting</p> <p>Follow-up time 1-14 days post-partum</p> <p>Arm 1 Sample size 12 mean 19.75 SD (15.45)</p> <p>Arm 2 Sample size 15 mean 23.4 SD (18.32)</p>
<p>Helland et al., 2008⁸⁰</p> <p>Study name: NR</p>	<p>Study Population: Healthy infants Healthy pregnant women Breast-feeding women</p>	<p>Inclusion Criteria: Healthy nulliparous or primiparous women, aged 19-35 with single</p>	<p>Start time: Pregnant week 18 of pregnancy</p> <p>Duration: NR</p>	<p>Outcome K-ABC: mental processing composite</p> <p>Follow-up time 4 years</p> <p>Arm 1 Sample size 28 mean 102</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study dates: 1994-2003</p> <p>Study design: Trial randomized parallel</p> <p>Location: Norway</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: 7 years 6729, 10331: both in original report; and 10608 (biomarkers)</p> <p>Follow-up article(s) ^{52, 87, 88}</p>	<p>Infants enrolled 262 Infants completers 143</p> <p>Pregnant age: cod oil 28.6 n=175 corn oil 27.6 n=166 (cod oil 3.4; corn oil 3.2)</p> <p>Race of Mother: NR (100)</p>	<p>pregnancies</p> <p>Exclusion Criteria: Unhealthy neonates</p>	<p>Arm 1: Cod oil Manufacturer Peter Moller, Avd Orkla ASA, Oslo, Norway Active ingredients Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively N-3 Composition. DHA 1183mg/10 mL EPA 803 mg/10mL Total N-3 2494 mg/10mL</p> <p>Arm 2: corn oil Active ingredients Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively ALA 92 mg/10mL</p>	<p>Arm 2 Sample size 30 mean 107 Follow-up time 7 years Arm 1 Sample size 28 mean 108 Arm 2 Sample size 30 mean 110 Outcome K-ABC: non-verbal abilities Follow-up time 4 years Arm 1 Sample size 28 mean 102 Arm 2 Sample size 30 mean 107 Follow-up time 7 years Arm 1 Sample size 28 mean 112 Arm 2 Sample size 30 mean 112 Outcome K-ABC: sequential processing Follow-up time 4 years Arm 1 Sample size 28 mean 107 Arm 2 Sample size 30 mean 109 Follow-up time 7 years Arm 1 Sample size 28 mean 105 Arm 2 Sample size 30 mean 107 Outcome K-ABC: simultaneous processing Follow-up time 4 years Arm 1 Sample size 28 mean 98 Arm 2 Sample size 30 mean 102 Follow-up time 7 years Arm 1 Sample size 28 mean 110 Arm 2 Sample size 30 mean 110</p>
<p>Tofail et al., 2006⁸¹</p> <p>Study name: NR</p> <p>Study dates: enrollment January to March 2000</p> <p>Study design: Trial randomized parallel</p> <p>Location: Bangladesh</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 10 months</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 400 Pregnant completers 151</p> <p>Pregnant age: 22.7 years (4.35 years) NR</p> <p>Race of Mother: Asian (100%)</p>	<p>Inclusion Criteria: seems as if all pregnant women at 25 weeks gestation were enrolled, no inclusion criteria specified</p> <p>Exclusion Criteria: NR</p>	<p>Start time: Pregnant 25 weeks gestation</p> <p>Duration: Pregnant until birth</p> <p>Arm 1: placebo Description soy oil capsule N-3 Composition. Dose 4 one gram capsules per day Blinding capsules were identical in appearance Other dose 1 LNA 0.27 g Other dose 2 linoleic acid 2.25 g</p> <p>Arm 2: DHA supplement Description fish oil capsules Dose 4 one gram capsules per day DHA 1.2 g EPA 1.8 g</p>	<p>Outcome BSID II Mental development index Follow-up time 10 months Arm 1 Sample size 124 mean 101.5 SD (7.8) Arm 2 Sample size 125 mean 102.5 SD (8) Outcome BSID II Psychomotor development index Follow-up time 10 months Arm 1 Sample size 124 mean 100.5 SD (10.1) Arm 2 Sample size 125 mean 101.7 SD (10.9)</p>
Campoy et al., 2011 ¹⁴²	Study Population:	Inclusion Criteria: health	Start time: Pregnant 22 weeks gestation Infants 22	Outcome Kauffman Assessment Battery for

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study name: NUHEAL</p> <p>Study dates: NR, <2011</p> <p>Study design: Trial randomized factorial design</p> <p>Location: Germany, Spain, Hungary</p> <p>Funding source / conflict: Government, None</p> <p>Follow-up: 6.5 years 3175, 3386</p> <p>Follow-up article(s) ¹⁴⁵, ¹⁴⁶</p>	<p>Healthy pregnant women</p> <p>Pregnant enrolled 315 Pregnant completers 154</p> <p>Pregnant age: 31 years (NR)</p> <p>Race of Mother: White European (99%)</p>	<p>pregnant women, singleton pregnancy, gestation 20 week at enrollment, body weight between 50 and 92 kg at study entry, and intention to deliver in one of the obstetrical centers</p> <p>Exclusion Criteria: serious chronic illness (eg, diabetes, hepatitis, or chronic enteric disease), use of FO supplements since the beginning of pregnancy or folate or vitamin B-12 supplements after gestation week 16</p>	<p>weeks gestation</p> <p>Duration: Pregnant until birth Infants until birth</p> <p>Arm 1: placebo Description milk-based supplement Brand name Blemil Plus Manufacturer Ordesa Laboratorios, Barcelona, Spain) Active ingredients vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose one daily dose of 15 g Blinding supplements were not distinguishable with respect to the appearance of the sachets or to their contents Maternal conditions Current smoker during pregnancy 8.9%</p> <p>Arm 2: fish oil Description fish oil in milk-based supplement Manufacturer Pronova Biocare, Lysaker, Norway Active ingredients vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose one 15 g dose Maternal conditions DHA 500 mg EPA 100 mg Current smoker during pregnancy 18.9%</p> <p>Arm 3: folic acid Description 400 ug 5-MTHF Manufacturer BASF, Ludwigshafen, Germany Active ingredients vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose one 15 g dose Maternal conditions Current smoker during pregnancy 17.1%</p> <p>Arm 4: folic acid + fish oil Description 400 _x0001_g 5-MTHF +fish oil Manufacturer BASF, Ludwigshafen, Germany Active ingredients vitamins and minerals in amounts meeting the recommended intakes during the</p>	<p>Children: Mental Processing Composite Follow-up time 6.5 years Arm 1 Sample size 45 median 110 IQR (14.5) Arm 2 Sample size 37 median 110 IQR (11) Arm 3 Sample size 35 median 108 IQR (12) Arm 4 Sample size 37 median 108 IQR (10.5) Outcome Kauffman Assessment Battery for Children: Sequential Processing Scale Follow-up time 6.5 years Arm 1 Sample size 45 median 106 IQR (19) Arm 2 Sample size 37 median 108 IQR (12) Arm 3 Sample size 35 median 104 IQR (14) Arm 4 Sample size 37 median 104 IQR (17) Outcome Kauffman Assessment Battery for Children: Simultaneous Processing Scale Follow-up time 6.5 years Arm 1 Sample size 45 median 112 IQR (11.5) Arm 2 Sample size 37 median 112 IQR (10.5) Arm 3 Sample size 35 median 109 IQR (14) Arm 4 Sample size 37 median 110 IQR (10.5)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			second half of pregnancy for European women Dose one 15 g dose Maternal conditions DHA 500 mg EPA 100 mg Current smoker during pregnancy 18.9%	
<p>Isaacs et al., 2011⁹⁵</p> <p>Study name: Unnamed Trial A</p> <p>Study dates: Recruitment of infants from 1995 through 1997 with 10-year followup</p> <p>Study design: Trial randomized parallel</p> <p>Location: UK</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: 10 years⁹⁶ reports growth outcomes at 10 years,⁹⁷ is original study, also⁹⁴ reports post-partum depression</p> <p>Follow-up article(s)⁹⁶ reports growth outcomes at 10 years,⁹⁷ is original study,⁹⁴</p>	<p>Study Population: Preterm infants</p> <p>Infants enrolled 238 Infants completers 107</p> <p>Infant age: birth (at < 35 weeks gestation) NA</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: birth weight of < 2000 g, and gestational age of < 35 weeks</p> <p>Exclusion Criteria: congenital malformations</p>	<p>Start time: Infants at hospital discharge</p> <p>Duration: Infants 9 months</p> <p>Arm 1: control Description control formula Active ingredients protein, minerals, vitamins A, E, K, D N-3 Composition. DHA 0 EPA 0 AA 0 Other dose 1 C18:2, n-6, linoleic acid 11.5 g / 100g fat Other dose 2 C18:3, n-3, alpha_x0004_-linolenic acid 1.6 g / 100g fat Arm 2: Omega 3 supplemented formula Description LCPUFA-Supplemented Formula Active ingredients protein, minerals, vitamins A, E, K, D Infant conditions DHA 0.5 g / 100g fat EPA 0.1 g / 100g fat AA 0.04 g / 100g fat Other comment 1 C18:2, n-6, linoleic acid 12.3 g / 100g fat Other comment 2 C18:3, n-6, gamma-linolenic acid 0.9 g / 100g fat Other comment 3 C18:3, n-3, _x0004_alpha-linolenic acid 1.5 g / 100g fat</p>	<p>Outcome Wechsler Abbreviated Scale of Intelligence: FSIQ Follow-up time 10 years Arm 1 Sample size 57 mean 92.7 SD (12.3) Arm 2 Sample size 50 mean 95.1 SD (13.2) Outcome Wechsler Abbreviated Scale of Intelligence: Performance IQ Follow-up time 10 years Arm 1 Sample size 57 mean 94.5 SD (14.1) Arm 2 Sample size 50 mean 94.2 SD (12.7) Outcome Wechsler Abbreviated Scale of Intelligence: VIQ Follow-up time 10 years Arm 1 Sample size 57 mean 92.6 SD (12.6) Arm 2 Sample size 50 mean 96.7 SD (13.2)</p>
<p>Jensen et al., 2010¹²⁰</p> <p>Study name: Unnamed Trial B</p> <p>Study dates: NR (<2010)</p>	<p>Study Population: Breast-feeding women</p> <p>Lactating enrolled 227</p> <p>Infants enrolled 230</p>	<p>Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age >=37 wk, infant birth weight between 2500 and 4200</p>	<p>Start time: Infants birth</p> <p>Duration: Infants 4 months</p> <p>Arm 1: placebo Description capsule containing corn & soy oil</p>	<p>Outcome Wechsler Primary and Preschool Scale of Intelligence - Revised : Vocabulary Subset Follow-up time 5 years Arm 1 Sample size 57 mean 12.9 SD (2.4) Arm 2 Sample size 60 mean 12.3 SD (2.8)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study design: Trial randomized parallel</p> <p>Location: US</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: 5 years ¹²¹</p> <p>Follow-up article(s) ¹²¹</p>	<p>Infants completers 119</p> <p>Lactating enrolled 227</p> <p>Lactating age: 31.5 years (5 years) 18 to 40</p> <p>Infant age: birth (NA) NA</p> <p>Race of Mother: NR (NR)</p>	<p>g</p> <p>Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant</p>	<p>Manufacturer Martek Biosciences</p> <p>Purity Data 50:50 mixture of soy and corn oils consisting, by weight, of 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18:2 n-6) and 3.9% a-linolenic acid (18:3 n-3) N-3 Composition.</p> <p>Dose 1 capsule</p> <p>Blinding capsules were identical</p> <p>ALA 3.9%</p> <p>Arm 2: omega 3 capsule</p> <p>Description high-DHA algal triglyceride capsule</p> <p>Brand name DHASCO</p> <p>Manufacturer Martek</p> <p>Purity Data by weight, 44% saturated fatty acids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n-6) and 41.7% DHA (22:6n-3)</p> <p>Dose 1 capsule</p> <p>DHA 200 mg</p>	<p>Outcome Wechsler Primary and Preschool Scale of Intelligence - Revised : Animal Pegs Subset</p> <p>Follow-up time 5 years</p> <p>Arm 1 Sample size 57 mean 12.2 SD (1.8)</p> <p>Arm 2 Sample size 60 mean 12.1 SD (2.4)</p> <p>Outcome Wechsler Primary and Preschool Scale of Intelligence - Revised : Block Design Subset</p> <p>Follow-up time 5 years</p> <p>Arm 1 Sample size 57 mean 11.1 SD (2.2)</p> <p>Arm 2 Sample size 60 mean 11.3 SD (2.1)</p> <p>Outcome Wechsler Primary and Preschool Scale of Intelligence - Revised : Information Subset</p> <p>Follow-up time 5 years</p> <p>Arm 1 Sample size 57 mean 11.2 SD (2.6)</p> <p>Arm 2 Sample size 60 mean 10.8 SD (2.6)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Ane C. Westerberg et al., 2011¹¹⁵</p> <p>Study name: Unnamed Trial D</p> <p>Study dates: Enrollment December 2003 and October 2005</p> <p>Study design: Trial randomized parallel</p> <p>Location: Norway</p> <p>Funding source / conflict: Manufacturer supplied product</p> <p>Follow-up: 20 months¹⁰³</p> <p>Follow-up article(s)¹⁰³</p>	<p>Study Population: Preterm infants</p> <p>Infants enrolled 141 Infants completers 92</p> <p>Mother age: Intervention: 30.8 years Control: 31.7 years (Intervention: 4.9 years Control: 5.0 years) 28-35 years</p> <p>Infant age: Mean Gestational age: Intervention: 28.7 weeks Control: 28.9 weeks (Intervention: 2.9 weeks Control: 2.7 weeks) Gestational age: 26.6-30.9 weeks</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: All VLBW infants (<1500g) born between December 2003 and November 2005 at Rikshospitalet-Radiumhospitalet Medical Center, Akershus University Hospital, Buskerud Hospital, and Vestfold Hospital in Norway</p> <p>Exclusion Criteria: Major congenital abnormalities or cerebral hemorrhage (grade 3 or 4) as determined through ultrasonography</p>	<p>Start time: Infants at start of enteral feeding</p> <p>Duration: Infants until discharge or until the study oil bottle was empty (mean duration of supplementation was 63 days)</p> <p>Arm 1: Placebo Description Soy oil Active ingredients 127mg linolenic acid/100 ml milk(27.1% total fatty acids) N-3 Composition. Dose 0.5 ml study oil/100 ml human milk Blinding Study oils packed in numbered bottles in hospital pharmacy ALA 16mg/100 ml milk; 3.4% total fatty acids Arm 2: DHA + AA group Description DHA and AA-containing oil Manufacturer Martek Active ingredients 88mg/100 ml linoleic acid per 100 ml milk (18.8%) Dose 0.5 ml study oil per 100 ml milk, ad lib Maternal conditions ALA 11mg/100 ml milk; 3.4% total fatty acids DHA 32mg/100ml milk (6.9%) AA 31 mg/100 ml milk (6.7% total fatty acids Current smoker 22% during pregnancy</p>	<p>Outcome Bayley Mental Development Index Follow-up time 20 months Arm 1 Sample size 42 mean 82.9 SD (13.3) Arm 1 Sample size 42 mean 100.5 SD (12.6) Arm 2 Sample size 40 mean 83.5 SD (10.5) Arm 2 Sample size 40 mean 102.6 SD (10.4) Outcome Bayley Mental Development Index (MDI) Follow-up time 20 months Arm 1 Sample size 42 mean 82.9 SD (13.3) Arm 2 Sample size 40 mean 83.5 SD (10.5)</p>
<p>Henriksen et al., 2008¹⁰³</p> <p>Study name: Unnamed Trial D</p> <p>Study dates: 2003-2006</p> <p>Study design: Trial randomized parallel</p> <p>Location: Norway</p> <p>Funding source / conflict: Manufacturer supplied product</p>	<p>Study Population: Preterm infants</p> <p>Infants enrolled 141 Infants completers 129</p> <p>Mother age: Median: Intervention: 31 years Control: 32 years 28-35 years</p> <p>Infant age: Median Gestational age: Control: 28.9 weeks Intervention: 28.4 weeks Gestational age: 26.6-30.9 weeks</p>	<p>Inclusion Criteria: All VLBW infants (<1500g) born between December 2003 and November 2005 at Rikshospitalet-Radiumhospitalet Medical Center, Akershus University Hospital, Buskerud Hospital, and Vestfold Hospital in Norway</p> <p>Exclusion Criteria: Major congenital abnormalities or cerebral hemorrhage (grade 3 or 4, as</p>	<p>Start time: Infants (intervention began when the infant received most of his nutrients enterally: >100ml human milk/kg body weight/day</p> <p>Duration: Infants Until discharge or bottle of study oil was empty (average 63 days of age)</p> <p>Arm 1: Control Description Study oil: soy oil and medium chain triglycerides Active ingredients 127mg linolenic acid/100 ml milk(27.1% total fatty acids) N-3 Composition. Dose 0.5 ml study oil/100 ml human milk Blinding Study oils packed in numbered bottles in hospital pharmacy</p>	<p>Outcome Ages and Stages Follow-up time 6 months Arm 1 Sample size 55 mean 215 SD (39) Arm 1 Sample size 55 mean 46.6 SD (9.1) Arm 1 Sample size 55 mean 30.9 SD (11.1) Arm 1 Sample size 55 mean 45.8 SD (14.3) Arm 1 Sample size 55 mean 49.5 SD (9.5) Arm 1 Sample size 55 mean 42.2 SD (12.3) Arm 2 Sample size 50 mean 221 SD (32) Arm 2 Sample size 50 mean 45.4 SD (7.9) Arm 2 Sample size 50 mean 33.3 SD (11.5) Arm 2 Sample size 50 mean 45.2 SD</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Follow-up: 6 months ¹¹⁵ Follow-up article(s) ¹¹⁵	Race of Mother: White European (Intervention: 79%; Control 84%)	determined through ultrasonography)	ALA 16mg/100 ml milk; 3.4% total fatty acids Arm 2: Intervention Description DHA and AA-containing oil Manufacturer Martek Biosciences Active ingredients 88mg/100 ml linoleic acid per 100 ml milk (18.8%) Dose 0.5 ml study oil per 100 ml milk, ad lib Maternal conditions Infant conditions DHA 32mg/100ml milk (6.9%) AA 31 mg/100 ml milk (6.7% total fatty acids Current smoker 22% during pregnancy	(10.7) Arm 2 Sample size 50 mean 53.4 SD (7) Arm 2 Sample size 50 mean 43.2 SD (12.8)

Table 18. Observational studies for Cognitive development

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Keim, et al., 2012¹⁴¹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: US</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Breast-feeding women</p> <p>Pregnant enrolled 1,169 Pregnant completers 689</p> <p>Infants enrolled 408 Infants completers 358</p> <p>Pregnant age: NR NR</p> <p>Infant age: 20 weeks gestation NA</p> <p>Race of Mother: White European (79.1%)</p>	<p>Inclusion Criteria: health women at less than 20 weeks of pregnancy</p> <p>Exclusion Criteria: pregnant with multiple fetuses, unable to communicate in English, under age 16 years, no access to a telephone, intention to go elsewhere for future care or delivery</p>
<p>Guxens, et al., 2011¹²⁷</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Spain</p> <p>Funding source / conflict: Government</p> <p>Follow-up: ¹²⁸</p>	<p>Study Population: Breast-feeding women</p> <p>Pregnant enrolled 657 Pregnant completers 622</p> <p>Lactating enrolled 622 Lactating completers 582</p> <p>Infants enrolled 622 Infants completers 582 (319 with LCPUFA data)</p> <p>Lactating enrolled 622 Lactating completers 582</p> <p>Lactating age: 31.6 years (4.2 years)</p> <p>Infant age: 2 to 5 days post partum</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: age older than 16 years, intent to deliver at the reference hospital, singleton pregnancy</p> <p>Exclusion Criteria: no problems of communication, no assisted conception</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Jordi Julvez, et al., 2014¹²⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Spain</p> <p>Funding source / conflict: Government</p> <p>Follow-up: ¹²⁷</p>	<p>Study Population: Breast-feeding women</p> <p>Pregnant enrolled 657 Pregnant completers 622</p> <p>Lactating enrolled 622 Lactating completers 582</p> <p>Infants enrolled 622 Infants completers 434</p> <p>Lactating enrolled 622 Lactating completers 582</p> <p>Lactating age: 31.6 years (4.2 years)</p> <p>Infant age: 2 to 5 days after birth</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: age older than 16 years, intent to deliver at the reference hospital, singleton pregnancy</p> <p>Exclusion Criteria: no problems of communication, no assisted conception</p>
<p>Bernard, et al., 2013¹¹⁷</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: NR</p> <p>Funding source / conflict: Industry, Government</p> <p>Follow-up: Ref 20 in this article</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 2,002 Pregnant completers 1,882</p> <p>Infants enrolled 1,882 Infants completers 1,510</p> <p>Pregnant age: 29.2 years (at conception) (4.8 years) NR</p> <p>Infant age: < 24 weeks gestation (NR) NR</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: < 24 weeks amenorrhea</p> <p>Exclusion Criteria: multiple pregnancies, known diabetes before pregnancy, illiteracy, and intention to move outside the region in the next 3 years</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Sun, et al., 2010¹¹⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Denmark</p> <p>Funding source / conflict: Government</p> <p>Follow-up: Unknown</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 65,754</p> <p>Infant age: birth</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: live-born singletons whose mothers provided information on fish intake from food frequency questionnaire</p> <p>Exclusion Criteria: children with missing information on maternal smoking and parity, children who died during the neonatal period, and children born to mothers with an unlikely high (>16,700 kJ/day) or low (<4200 kJ/day) intake of energy during pregnancy</p>
<p>Bakker, et al., 2003¹²⁹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Government</p> <p>Follow-up: ¹¹⁹ and two articles in original report: see above</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 750 Infants withdrawals 444 Infants completers 306</p> <p>Pregnant age: 29.8 (4.1)</p> <p>Infant age: birth</p> <p>Race of Mother: White European (100)</p>	<p>Inclusion Criteria: 750 Caucasian children of 7 y old, born between December 1990 and January 1994 in the course of an earlier study on maternal and neonatal LCPUFA status and pregnancy outcome</p> <p>Exclusion Criteria: Not reported</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Steer, et al., 2013¹⁴³</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: UK</p> <p>Funding source / conflict: Government</p> <p>Follow-up: unsure</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 14,541</p> <p>Infants completers 2,839</p> <p>Mother age: 29.33 (4.48)</p> <p>Infant age: birth</p> <p>Race of Mother: White European (98.8) Black (0.6) Asian (0.6)</p>	<p>Inclusion Criteria: pregnant women with expected delivery date between 4/91 and 12/92 in Bristol UK</p> <p>Exclusion Criteria: Not reported</p>

Autism Spectrum Disorders (ASD)

Randomized Controlled Trials

The original report did not include ASD as an outcome of interest. No RCTs (including long term follow-ups) that reported ASD as an outcome were identified for the current report.

Observational Studies

One observational study¹⁴⁷ investigated whether n3 FA intake before and during pregnancy was associated with risk of ASD in offspring. Lyall et al (2013) conducted an analysis of data from the Nurses Health Study II. They compared dietary intake between 317 mothers of children with ASD and 17,728 comparison mothers. Children were born from 1991 through 2007. Prepregnancy and pregnancy dietary information was reported via food frequency questionnaire (FFQ) and ASD diagnosis was self-reported by mothers. The authors found that women with the highest quartile of total PUFA intake were at lower risk of having a child with ASD than women in the lowest quartile (RR 0.67; 95% CI 0.49, 0.92). This model adjusted for maternal age, income level, race, BMI, total energy intake, pre-pregnancy smoking status, and child's year of birth. Using the same model and adjustments, the researchers also found that women whose intake of linoleic acid was in the highest quartile had a lower risk of having a child with ASD than those in the lowest quartile (RR 0.66 95% CI 0.48, 0.92). The authors advised that the results should be interpreted with caution, given the small number of cases.

Table 19. Observational studies for Autism

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Lyall, et al., 2013¹⁴⁷</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: NR</p> <p>Location: US</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 18,045 Pregnant completers 5,884</p> <p>Pregnant age: 34 years NR</p> <p>Infant age: birth</p> <p>Race of Mother: White European (97%)</p>	<p>Inclusion Criteria: female nurses who were 25–42 years of age in 1989, with index births between 1991 (the year of first collection of dietary information) and 2007</p> <p>Exclusion Criteria: women without food frequency questionnaire data or without autism diagnosis info on child</p>

Learning Disorders and ADHD

The outcomes of learning disorders and attention deficit-hyperactivity disorder (ADHD) are additional outcomes of interest that were not included in the original report. No studies were identified for these outcomes for the current report.

Atopic Dermatitis and Eczema

Key Points

- In four prenatal n-3 interventions and two follow-up studies, there was conflicting evidence on the association between maternal n-3 FA supplementation (DHA + EPA, varying doses) and eczema. Two studies found no significant association while others found decreasing risk of eczema with n-3 FA supplementation. However, in most cases where there was significant association, the relationship was no longer observed or became marginal after adjusting for potential confounders or after long-term follow-up. Finally, meta-analysis of three RCTs (n=366) with 12 month follow-up of eczema outcomes yielded a non-significant summary effect. A single trial with ALA supplementation also found no relationship.
- In three postnatal n-3 interventions and two follow-up studies, there was no association between infant n-3 FA supplementation (DHA or DHA+EPA, varying doses) and eczema prevalence up to 5 years of age.
- One biomarker study found associations between higher infant plasma DHA, erythrocyte EPA and EPA/AA ratio and lower risk of eczema as well as increased symptoms of eczema with higher levels of AA and total n-6 PUFA.
- Six of seven prospective observational studies found no associations between n-3 FA exposure (measured through maternal dietary intake or breast milk composition) and eczema. One of three prospective observational studies of n-3 FA biomarkers (in cord blood or maternal blood sample) found decreased risk of eczema and increasing AA levels, with null findings for the remaining two studies.

This outcome is an additional outcome of interest that was not included in the original review. A total of 12 eligible studies (8 original RCTs and 4 follow-up studies) and 10 observational studies were identified for this report. The study population included healthy pregnant women and infants with history of allergy as well as preterm infants.

Randomized Controlled Trials

Prenatal maternal interventions/exposures

We identified seven studies (5 RCTs and 2 follow-up studies) that evaluated n-3 FA interventions given to the mothers during the prenatal period.^{48, 53, 57, 82, 148-150} Among these studies, five studies assessed interventions with duration from pregnancy until birth.^{48, 53, 57, 58, 150} Three studies with maternal supplementation started during pregnancy and continued into breastfeeding,^{82, 148, 149} with one of those trials also adding infant supplementation following breastfeeding.⁸² All of these trials except for one⁸² recruited pregnant women whose infants were at risk of atopy (e.g., one or more first-degree relatives of the infant affected by atopy, asthma or allergy).

DHA + EPA vs. placebo

Six RCTs compared EPA plus DHA versus placebo.^{48, 53, 57, 148-150}

Dunstan et al. (2003) randomized 98 pregnant, atopic Australian women to fish oil (3.7g n-3 PUFA, 56.0% DHA, 27.7% EPA) or placebo (olive oil [4g]) daily from 20 weeks gestation until delivery.⁵⁷ A total of 83 mothers and their children completed the 12-month follow-up. The

authors report that infants in the fish oil group had higher odds of eczema, although this increase in risk is not statistically significant (OR 1.88, 95% CI 0.77, 4.65; $p=0.167$). In addition, of the infants with eczema, those in the fish oil group were less likely to have severe disease, defined as a modified SCORAD index >25 , than those in the placebo group (OR=0.09; 95% CI 0.01, 0.94; $p=0.045$).⁵⁷

In the Salmon in Pregnancy Study (SiPS), 123 pregnant women in the UK were randomized to the salmon group (300g salmon / week) or control group (no changes in diet) from 20 weeks gestation until delivery.¹⁵⁰ Clinical outcomes were available for 86 infants at 6 months. No differences in the incidence or severity (using the SCORAD index) of atopic dermatitis were observed between the salmon and control groups.¹⁵⁰

In a subset of the Docosahexaenoic Acid (DHA) to Optimise Mother Infant Outcome (DOMInO) trial, 706 pregnant Australian women whose child was at high risk for genetic allergy were randomized to an n-3 LCPUFA group (800 g/d DHA + 100 g/d EPA) or placebo group (vegetable oil) from 21 weeks gestation until delivery.^{48, 53} In a 1-year follow-up study, the n-3 LCPUFA group showed an unadjusted decrease in the risk for eczema with sensitization, however, once adjusted for study center, parity, maternal history, and sex, this difference was only marginal (RR 0.64; 95% CI 0.40, 1.03; $p=0.06$).⁴⁸ In a longer follow-up, medical assessments were completed for 638 children (90.4%) at 3 years of age: No differences were seen between treatment groups for eczema with sensitization during the first 3 years of life (RR=0.75; 95% CI 0.53, 1.05) or at age 3 (RR=0.86, 95% CI 0.58, 1.27) in analyses adjusted and unadjusted for study center, parity, maternal history, and sex.⁵³

One RCT randomized 145 pregnant women in Sweden to daily n-3 FA (1.6g EPA + 1.1g DHA) or placebo (soy oil) supplementation from the 25th gestational week through the exclusive breastfeeding period (average 3-4 months). Period prevalence for the first 12 months of life was lower in infants of n-3 FA supplemented mothers in adjusted analyses for IgE-associated eczema, defined as clinical diagnosis of eczema and positive SPT/IgE to egg, milk, and/or wheat (OR 0.22, 95% CI 0.06-0.81).¹⁴⁹ In another follow-up study with 143 infants, no differences were observed in cumulative eczema through 24 months or current eczema at 24 months between the treatment groups. A significant difference in IgE-associated eczema was seen, favoring the EPA+DHA intervention (9% vs 24%, $p=0.04$); however this difference became marginal in an adjusted multiple regression model (OR 0.33; 95% CI 0.1, 1.1, $p=0.06$).¹⁴⁸

Meta-analysis of three RCTs with a 12 month follow-up^{58, 149, 150} yielded a non-significant summary effect size for DHA supplementation and risk of eczema (OR = 0.52, 95% CI 0.15-1.81, $I_2=0\%$) (**Figure X**).

ALA vs. placebo

We identified a single trial that examined ALA supplementation during pregnancy, breastfeeding, and infancy.⁸² Linnamaa et al. (2010) randomized 313 pregnant Finnish women (<16 weeks gestation) to blackcurrant seed oil (14% ALA by weight of 3g/d) or olive oil (placebo). The first dose was administered between the 8th and 16th week of pregnancy and continued during breastfeeding. Once the exclusive breastfeeding period was over, infants received 1 mL/day of supplemental oil until age 2 years. Of the 313 mother-infant pairs, 241 were analyzed at 3 months, 210 at 12 months, and 177 at 24 months. No differences were seen in prevalence of atopic dermatitis at 3 months or 24 months. However, at 12 months, fewer cases of atopic dermatitis were noted (33.0% vs 47.3%, $p=0.035$) and severity of symptoms was lower ($p=0.035$) in the ALA group compared to the placebo.

Postnatal maternal or infant interventions/exposures

Three RCTs and two follow-up studies evaluated maternal n-3 FA interventions during the postnatal period.^{112, 125, 151-153} One of the RCTs evaluated preterm infants¹¹² while the remaining assessed term infants who were at genetic risk for allergy. All RCTs evaluated DHA DHA+EPA.

DHA, DHA + EPA vs. placebo

One RCT began the n-3 FA intervention during the postnatal period.¹¹² The DINO trial randomized 657 preterm Australian infants (<33 weeks gestation) to receive a high-DHA diet (~1% DHA and 0.6% AA) or standard DHA diet (~0.35% DHA and 0.6% AA) through breast milk or formula until their expected delivery date. Eczema data were available for 232 infants at 12 months and 292 infants at 18 months. No differences were seen in the risk for eczema (adjusted or unadjusted for gestational age at delivery and gender).¹¹²

In the Infant Fish Oil Supplementation Study (IFOS), 420 infants at high risk for atopy were randomized to daily fish oil capsules (280 mg DHA + 110 mg EPA) or placebo capsules (olive oil) from birth to 6 months. At 12 months, no significant overall difference in eczema was seen between the fish oil and placebo groups, however in infants in the highest adherence quartile, the fish oil group had a lower prevalence of eczema ($p=0.041$).¹²⁵

In the Childhood Asthma Prevention Study (CAPS), 616 pregnant women (<36 weeks gestation) whose child was at high risk for developing asthma were randomized into 4 groups, including 2 with a dietary component (500 mg tuna fish oil supplement + canola-based oils and spreads or placebo supplement + polyunsaturated oils and margarines) from 6 months. In an 18-month follow-up with 543 infants (88% of the total sample size), no significant difference in prevalence of eczema or dermatitis was seen by parental report or nurse examination between the diet intervention and control groups.¹⁵¹ In a 3-year follow-up with 526 infants, no difference was observed between the diet and control groups for prevalence of eczema.¹⁵³ In a 5-year follow-up with 516 children (84%), the diet intervention and control groups did not differ significantly in risk for current eczema ($RR=0.85$; 95% CI 0.61, 1.17).¹⁵²

Biomarker Studies

Biomarker associations were also captured in the previously mentioned IFOS trial.¹²⁵ Infants with higher erythrocyte EPA composition ($P = .033$) and higher EPA/AA ratio ($P = .022$) as well as higher plasma DHA levels ($P = .047$) at 6 months of age were significantly less likely to develop eczema by 12 months. In addition, higher levels of AA ($P = .004$) and total n-6 PUFA ($P = .005$) levels at 6 months were associated with increased symptoms of eczema (recurrent dry, itchy, red and scaly patches of skin) at 6 months of age.¹²⁵

Observational Studies

Ten observational studies were identified that evaluated the association between some measure of n-3 FA exposure and risk of atopic dermatitis/eczema.¹⁵⁴⁻¹⁶³

All studies enrolled populations of healthy infants except for one¹⁵⁹ that enrolled infants with human leucocyte antigen (HLA)-conferred susceptibility to type I diabetes. All the studies were prospective cohort studies. The range of exposures included maternal dietary intake of n-3 FA,¹⁵⁹⁻¹⁶² breast milk n-3 FA,^{154, 157, 163} and maternal biomarkers.^{155, 156, 158} Publications dated from 2004 to 2014.

n-3 FA Intake

Four studies evaluated the association between maternal dietary n-3 FA intake and risk of atopic dermatitis.¹⁵⁹⁻¹⁶²

In a 2009 study of 763 healthy mother-infant pairs from the Osaka Maternal and Child Health Study in Japan, there was no significant association detected between maternal intake of n-3 fatty acids during pregnancy and risk of eczema in the offspring.¹⁶¹ Maternal dietary intake was assessed with a validated diet history questionnaire during pregnancy while eczema was assessed by maternal report based on the International Study of Asthma and Allergies in Childhood for offspring at 16-24 months postpartum.

A 2010 study of 771 healthy Japanese infants aged 3-4 months found no relationship between maternal intake of n-3 FAs during pregnancy (calculated based on a validated diet history questionnaire) and risk of atopic eczema.¹⁶⁰

A 2012 study assessed the association between maternal n-3 FA intake in a cohort of 2,441 newborn infants born between 1997 and 2004 in Finland and atopic dermatitis after 5 years of follow-up. Enrolled infants had a history of human leucocyte antigen (HLA)-conferred susceptibility to type I diabetes. No significant difference was observed in total maternal n-3 FA intake or n-3/n-6 FA ratio (assessed using a validated FFQ) between offspring who developed atopic eczema and those who did not.¹⁵⁹

Also, in a 2013 study of 1,354 healthy mother-infant pairs from the Kyushu Okinawa Maternal and Child Health Study (KOMCHS) in Japan, no significant association was detected between maternal intake of n-3 fatty acids during pregnancy and risk of eczema in the offspring.¹⁶² Maternal dietary intake was assessed with a dietary history questionnaire during pregnancy, whereas infantile eczema was assessed by parental report based on the International Study of Asthma and Allergies in Childhood for offspring at 23-29 months postpartum.

n-3 FA Breastmilk Intake

Three studies assessed the association of breast milk fatty acids with risk for atopic eczema.^{154, 157, 163}

A 2006 study of 265 mother-infant pairs in the Netherlands found no relationship between breast milk n-3 fatty acid concentration (measured at 3 months postpartum) and risk of atopic eczema in children at 1 year and 4 years of age. Similar results were found in children of mothers both with and without allergy.¹⁵⁴

However, in another 2011 study of 310 mother-infant pairs in the Netherlands, higher concentrations of breast milk n-3 fatty acid (EPA+DHA+DPA) were significantly associated with lower risk of developing atopic dermatitis (using the UK Working Party criteria [p for trend=0.024]) and parent-reported eczema (p for trend=0.040) at 2 years of age, adjusted for recruitment group, maternal age, maternal education, infant's gender, number of older siblings and their atopic history, parental atopic history, maternal smoking during pregnancy and/or smoking in presence of the infant, place of birth, season of breast milk collection and other potential confounders.¹⁵⁷

A 2012 study of 580 infants in Spain found no significant association between colostrum n-3 LC-PUFA and risk of atopic eczema during the first 14 months of life.¹⁶³ Only random samples of colostrum were collected for analysis (n=352), with n-3 LC-PUFA values imputed for the rest of the sample, however no differences were observed in analyses with the colostrum subsample only.

Blood n-3 FA Biomarkers

Three studies examined the association between n-3 FA biomarkers and risk of atopic dermatitis.^{155, 156, 158}

A 2004 study of 1238 mother-infant pairs conducted in the UK found a positive association between the ratio of AA: EPA in cord blood and risk of eczema at 18 to 30 months (adjusted odds ratio [OR] per doubling, 1.14; 95% CI, 1.00-1.31; P = .044). The association was however no longer significant after adjusting for multiple comparisons. No significant associations were observed for late pregnancy maternal plasma phospholipid n-3 fatty acid exposures (n=2945).¹⁵⁵

In a 2011 study of 1,275 children from the KOALA Birth Cohort Study who were followed for 6-7 years, low risk of eczema was associated with a higher ratio of maternal plasma phospholipid n-6 to n-3 LCPUFAs, measured at 34–36 weeks of pregnancy (p for trend = 0.012). In addition, a decreased risk of eczema in the first 7 months of life was observed with increasing arachidonic acid levels (p for trend = 0.013).¹⁵⁸

A 2014 study of 436 infants from the Munich LISApplus birth cohort study in Germany found no significant association between n-3 LC-PUFA or n-6/n-3 ratio in cord blood serum and eczema at 2, 6, and 10 years follow-up.¹⁵⁶

Observational study subgroup analyses

None of the studies reported subgroup analyses.

Table 20. RCTs for Atopic dermatitis

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Marks et al., 2006¹⁵²</p> <p>Study name: CAPS</p> <p>Study dates: 1997-2004</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 5 years</p> <p>Follow-up article(s) ^{164, 165, 151, 166, 153}</p>	<p>Study Population: Pregnant women with allergies</p> <p>Pregnant enrolled 616 Pregnant withdrawals 100 Pregnant completers 516</p> <p>Infants completers 516</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: pregnant women whose unborn children were at increased risk of developing asthma because 1 or more parents or siblings had asthma or wheezing</p> <p>Exclusion Criteria: with a pet cat at home, strict vegetarians, women with a nonsingleton pregnancy, and infants born earlier than 36 weeks of gestation. Infants had birth weights less than 2.5 kg, significant congenital malformations, or other significant neonatal disease.</p>	<p>Start time: Infants from the time the child started bottle-feeding, or to solid foods from age 6 months</p> <p>Duration: NR</p> <p>Arm 1: Diet control Description polyunsaturated oils and spreads, containing 40% w6 FA, and sunola oil capsules Manufacturer Crisco-Meadow Lea Foods Inc, Sydney, Australia Blinding The approach to blinding participants and research staff is described in this article's Online Repository at www.jacionline.org.</p> <p>Arm 2: Active Description canola-based oils and spreads, which are low in n-6 fatty acids, and tuna oil capsules, which contain n-3 fatty acids.</p>	<p>Outcome current eczema</p> <p>Follow-up time 5 years</p> <p>Arm 1 59/249 (23.69%)</p> <p>Arm 2 54/267 (20.22%)</p>
<p>Mihrshahi et al., 2003¹⁵¹</p> <p>Study name: CAPS</p> <p>Study dates: 1997-2002</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up: 18 months 1400</p>	<p>Study Population: Pregnant women with allergies</p> <p>Pregnant enrolled 616 (all 4 arms) Pregnant withdrawals 62 Pregnant completers 554</p> <p>Pregnant age: 28.5 (5.3)</p> <p>Race of Mother: NR (96.9%) Other race/ethnicity (Aboriginal 3.1%)</p>	<p>Inclusion Criteria: At least one parent or sibling with symptoms of asthma as assessed by screening questionnaire, Reasonable fluency in English, Telephone at home, Reside within 30 km from center of recruitment</p> <p>Exclusion Criteria: Pet cat at home, Families on strict vegetarian diet, Multiple births, Babies born earlier than 36 weeks gestation, with congenital malformations or other serious disease,</p>	<p>Start time: Infants initiation of bottle feeding or 6 months of age</p> <p>Duration: Infants NR</p> <p>Arm 1: Diet Control/HDM control or intervention Brand name Sunola oil Manufacturer Clover Corporation</p> <p>Arm 2: Dietary intervention/HDM control or intervention Description 500mg n-3 rich tuna fish oil supplement Manufacturer Clover Corporation N-3 Compositionsee Mihrshahi, 2004 table 4 (equivalen to breast milk)</p>	<p>Outcome eczema or dermatitis</p> <p>Follow-up time 18 months</p> <p>Arm 1 31/275 (11.11%)</p> <p>Arm 2 31/279 (11.11%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Follow-up article(s) ^{164, 165, 166, 152, 153}		or requiring major surgery or hospitalization for greater than 1 week		
Peat et al., 2004 ¹⁵³ Study name: CAPS Study dates: 2000-2003 Study design: Trial randomized factorial design Location: Australia Funding source / conflict: Industry, Government Follow-up: 3 years 3574, 9131 Follow-up article(s) ^{164, 165, 151, 166, 152}	Study Population: NR Pregnant enrolled 616 Pregnant withdrawals 90 Pregnant completers 526 Pregnant age: Placebo: 29.1 Diet: 28.6 (Placebo: 5.0 Diet: 5.3) NR Race of Mother: NR (100)	Inclusion Criteria: at least 1 parent or sibling with current asthma or frequent wheeze as assessed by screening questionnaire, fluency in English, a telephone at home, and residence within 30 km of the recruitment center. Exclusion Criteria: a pet cat at home, a vegetarian diet, multiple births, and less than 36 weeks gestation.	Start time: Infants 6 months of age Duration: Infants NR Arm 1: Placebo group Description The control group received placebo supplement capsules of Sunola oil containing 83% monounsaturated oils (Clover Corp) and were provided with widely used soybean-based polyunsaturated oils and margarines high in omega-6 fatty acids for use in all food preparation Manufacturer Clover Corp; Goodman Fielder Blinding The research team responsible for recruitment was blind to the methods of randomization until recruitment was complete. the research nurses and research assistants who undertook the outcome assessments, laboratory analyses, and statistical analyses were blind to the group allocation of the participants. Arm 2: Active intervention group Description tuna fish oil capsules Manufacturer Clover Corp; Goodman Fielder Dose 500 mg tuna fish oil capsules daily Total N-3 184 mg	Outcome any eczema Follow-up time 3 years Arm 1 157/259 (60.62%) Arm 2 132/267 (49.44%)
Manley et al., 2011 ¹¹² Study name: DINO Study dates: 2001-2007 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product, Some authors	Study Population: Preterm infants Breast-feeding women Infants enrolled 657 Infants completers 614 Lactating age: Intervention: 29.9 (5.8) Placebo: 30.2 (5.4) Infant age: 4 days (median) Race of Mother: NR	Inclusion Criteria: Infants born before 33 weeks' gestation, within 5 days of the infant commencing any enteral feedings. Exclusion Criteria: major congenital or chromosomal abnormalities, from a multiple birth in which not all live-born infants were eligible, enrolled in other trials of fatty acid supplementation, or	Start time: Infants Within 5 days (or less) of starting enteral feeding Duration: Infants NR Arm 1: Standard DHA diet Description Soy bean oil Manufacturer Clover Corporation Dose 6 capsules per day Maternal conditions Infant conditions Current smoker 25% during pregnancy Other maternal conditions 1arm_1_maternal_conditions_other1 Other maternal conditions 2 Birth by C-section: 69%	Outcome eczema Follow-up time 12 months Arm 1 40/249 (16.06%) Arm 2 29/232 (12.5%) Follow-up time 12 or 18 months Arm 1 67/248 (27.02%) Arm 2 61/236 (25.85%) Follow-up time 18 months Arm 1 51/311 (16.4%) Arm 2 48/292 (16.44%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>serve on scientific advisory boards for corporations</p> <p>Follow-up: 18 months see above</p> <p>Follow-up article(s) ^{111, 100, 113, 101, 114},</p>	(100%)	mother with contraindication to fish oil	<p>Pre-term birth 100%</p> <p>Low birth weight 18.6%</p> <p>Arm 2: High DHA</p> <p>Description Tuna fish oil</p> <p>Manufacturer Clover Corporation</p> <p>Dose 6 500-mg DHA-rich tuna oil capsules per day</p> <p>Maternal conditions</p> <p>Infant conditions</p> <p>DHA DHA to achieve a breast milk concentration that was 1% of total fatty acids</p> <p>Current smoker 25% during pregnancy</p> <p>Other maternal conditions</p> <p>1arm_2_maternal_conditions_other1</p> <p>Other maternal conditions 2 Birth by c-section: 68.3%</p> <p>Other comment 1 If supplementary formula was required, infants were given a high- DHA preterm formula (approximately 1.0%DHAand 0.6% AA).</p>	
<p>Palmer et al., 2012⁴⁸</p> <p>Study name: DOMInO</p> <p>Study dates: 2006-2009</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Industry, Government, Manufacturer supplied product</p> <p>Follow-up: 9415</p> <p>Follow-up article(s) ^{34, 49, 50, 51, 52, 53, 3},</p>	<p>Study Population: Pregnant women with allergies</p> <p>Pregnant enrolled 706 Pregnant withdrawals 25 Pregnant completers 681</p> <p>Infants enrolled 706 Infants withdrawals 25 Infants completers 681</p> <p>Pregnant age: Treatment: 29.6 Placebo: 29.5 (Treatment: 5.7 Placebo: 5.6) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Included if the unborn baby had a mother, father, or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) and they were enrolled from the Women's and Children's Hospital or Flinders Medical Centre in Adelaide.</p> <p>Exclusion Criteria: NR</p>	<p>Start time: Pregnant 21 weeks of gestation Infants 21 weeks of gestation</p> <p>Duration: Pregnant until delivery Infants till delivery</p> <p>Arm 1: Placebo</p> <p>Description 338 women assigned to control supplements-vegetable oil capsules</p> <p>Dose three 500 mg vegetable oil capsules daily</p> <p>Blinding All capsules were similar in size, shape, and colour. . Neither the women nor the research staff were aware of the treatment allocated.</p> <p>Arm 2: n-3 LCPUFA group</p> <p>Description 368 women assigned to fish oil concentrate</p> <p>Brand name Incr omega 500 TG</p> <p>Manufacturer Croda Chemicals, East Yorkshire, UK</p> <p>Dose e three 500 mg capsules daily</p> <p>DHA 800mg</p> <p>EPA 100mg</p>	<p>Outcome eczema with sensitization</p> <p>Follow-up time 1 year</p> <p>Arm 1 39/338 (11.54%)</p> <p>Arm 2 26/368 (7.07%)</p>
<p>Palmer et al., 2013⁵³</p> <p>Study name: DOMInO</p>	<p>Study Population: NR</p> <p>Pregnant enrolled 706 Pregnant completers 638</p>	<p>Inclusion Criteria: Women whose infants had a parent or sibling with a history of any</p>	<p>Start time: Pregnant <21 weeks gestation</p> <p>Duration: Pregnant to term</p>	<p>Outcome eczema</p> <p>Follow-up time 3 years</p> <p>Arm 1 64/338 (18.93%)</p> <p>Arm 2 15/368 (4.08%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study dates: 2006-2009 (allergy follow-up to Domino study)</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Industry, Government, Some authors serve on scientific advisory boards for corporations</p> <p>Follow-up: 3 years 3170, 3069</p> <p>Follow-up article(s) ^{34, 48, 49, 50, 51, 52, 3}</p>	<p>Infants enrolled 706 Infants completers 638</p> <p>Pregnant age: DHA: 28.9 Control: 28.9 (DHA: 5.7) Control: 5.6)</p> <p>Infant age: Birth</p> <p>Race of Mother: NR (100)</p>	<p>medically diagnosed allergic disease (asthma, allergic rhinitis, eczema)</p> <p>Exclusion Criteria: Already taking a prenatal supplement with DHA Fetus had a known major abnormality, Bleeding disorder in which tuna oil was contraindicated, Taking anticoagulant therapy A documented history of drug or alcohol abuse, Participating in another fatty acid trial, Unable to give written informed consent, or English was not the main language spoken at home</p>	<p>Arm 1: Control Description vegetable oil Dose 3 500-mg vegetable oil capsules per day Blinding This was a double-blinded study; all capsules were similar in size, shape and colour</p> <p>Arm 2: Fish oil Brand name Incromega 500 TG, Manufacturer Croda Chemicals, East Yorkshire, England Dose 3 500-mg capsules per day DHA 800 mg per day EPA 100 mg per day</p>	
<p>Dunstan et al., 2003⁵⁷</p> <p>Study name: Dunstan</p> <p>Study dates: 1999-2001</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 1 year 4381,6647</p> <p>Follow-up article(s) ^{42, 56, 58, 59}</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 98 Pregnant withdrawals 15 Pregnant completers 83</p> <p>Pregnant age: NR (NR) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: All women had a history of physician-diagnosed allergic rhinitis and/or asthma and 1 or more positive skin prick tests to common allergens (house dust mite; grass pollens; molds; and cat, dog, and cockroach extracts)</p> <p>Exclusion Criteria: Women were ineligible for the study if they smoked; if they had other medical problems, complicated pregnancies, or seafood allergy; or if their normal dietary intake exceeded</p>	<p>Start time: Pregnant 20 weeks of gestation</p> <p>Duration: Pregnant till delivery</p> <p>Arm 1: Placebo group Description 46 women allocated and received placebo-olive oil Manufacturer Pan Laboratories, Moorebank, NSW, Australia Active ingredients 66.6% n-9 oleic acid N-3 Composition. Dose 4 (1-g) capsules of olive oil per day Blinding Randomization and allocation of capsules occurred at a different center separate from the recruitment of participants. Capsules were administered to the participants by someone separate from those doing the allocation. The capsules in the 2 groups were image-matched. Total N-3 <1% n-3 PUFAs</p> <p>Arm 2: Fish oil group Description 52 women were randomized to receive fish oil</p>	<p>Outcome atopic dermatitis Follow-up time 1 year Arm 1 13/43 (30.23%) Arm 2 18/40 (45%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		2 meals of fish per week.	Manufacturer Ocean Nutrition, Halifax, Nova Scotia, Canada Dose 4 (1g) fish oil capsules per day _x001E__x0007__x0005__x0015__x0013__x0007__ _x001E__x0013__x000F_ DHA 56.0% EPA 27.7% Total N-3 3.7 g	
D'Vaz et al., 2012 ¹²⁵ Study name: IFOS Study dates: 2005-2009 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, None, Manufacturer supplied product Follow-up article(s) ¹²⁴ , Protocol ID 5460	Study Population: Pregnant women with allergies Infants enrolled 420 Infants completers 323 Pregnant age: Placebo: 33.2 Fish Oil: 32.5 (Placebo: 4.2 Fish Oil: 4.8) Infant age: Term (39.3 weeks gestation) Race of Mother: NR (100)	Inclusion Criteria: Maternal: Pregnant History of doctor diagnosed asthma or allergic rhinitis Skin prick positive to at least one allergen Exclusion Criteria: Maternal: Smoking Auto-immune disease Pre-existing medical conditions other than asthma High-risk pregnancy Seafood allergy Fish eaten more than three times per week Fish oil supplementation already taken (in excess of 1000 mg per day) Exclusion from data analysis criteria due to protocol deviations: Pre-term delivery (gestation <36 weeks) Infant with congenital abnormalities or significant disease not related to intervention	Start time: Infants Birth Duration: Infants 6 months Arm 1: Placebo Description Olive oil Manufacturer Ocean Nutrition, Ltd Dose 650 mg olive oil Blinding Randomization was completed by external staff via computer software using an unpredictable allocation sequence, stratified according to maternal and paternal atopic history and parity. Mothers and study personnel were unaware of the group allocation. Maternal conditions Maternal allergies 100 Arm 2: Fish oil group Manufacturer Ocean Nutrition Ltd. Purity Data fatty acid composition remained unchanged over the study period Dose 1 capsule contents, to be administered orally, prior to feeding in the morning Maternal conditions DHA 280 mg EPA 110 mg Maternal allergies 100	Outcome eczema Follow-up time 12 months Arm 1 68/167 (40.72%) Arm 2 61/156 (39.1%)
Furuhjelm et al., 2009 ¹⁴⁹ Study name: NR Study dates: 2003-2006	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 145	Inclusion Criteria: a family history of past of current allergic symptoms in at least one parent or older child.	Start time: Pregnant 25 weeks of gestation Duration: Pregnant 15 weeks (i.e., until delivery) Arm 1: Placebo	Outcome IgE associated eczema Follow-up time 12 months Arm 1 15/63 (23.81%) Arm 2 4/52 (7.69%) Follow-up time 6 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study design: Trial randomized parallel</p> <p>Location: Sweden</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 1 year 303</p> <p>Follow-up article(s) ^{148, 167}</p>	<p>Pregnant withdrawals 28 Pregnant completers 117</p> <p>Infants enrolled 145 Infants withdrawals 28 Infants completers 117</p> <p>Mother age: Intervention: 31.1 years (at delivery) Placebo: 31.7 years (at delivery) (Intervention: 4.1 years (at delivery) Placebo: 3.9 years (at delivery)) NR</p> <p>Race of Mother: NR (100)</p>	<p>Exclusion Criteria: Mothers with an allergy to soy or fish or undergoing treatment with anticoagulants or commercial w-3 fatty acid supplements</p>	<p>Description 75 women received soy oil as placebo Manufacturer Pharma Nord Active ingredients w-6 PUFA LA (58%, 2.5 g/day), a small amount (6%, 0.28 g/day) of the w-3 PUFA LNA and 36 mg a- tocopherol Viability alpha-tocopherol was given as an antioxidant, a necessary ingredient according to the standard procedure of the manufacturer to assure the durability of the oil. N-3 Composition. Dose nine soy oil capsules a day N-6 N-3 9 Arm 2: w3 group Description 70 women are randomized into this group Brand name Bio Marin capsules Manufacturer Pharma Nord, Vejle, Denmark Active ingredients 23 mg alpha-tocopherol Viability alpha-tocopherol was given as an antioxidant, a necessary ingredient according to the standard procedure of the manufacturer to assure the durability of the oil. Dose nine 500-mg capsules, once daily DHA 1.1g EPA 1.6g N-6 N-3 <0.1</p>	<p>Arm 1 13/65 (20%) Arm 2 4/52 (7.69%)</p>
<p>Furuhjelm et al., 2011 ¹⁴⁸</p> <p>Study name: NR</p> <p>Study dates: 2003-2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: Sweden</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 2 years 4378</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117</p> <p>Infants enrolled 145 Infants withdrawals 28 Infants completers 117</p> <p>Pregnant age: NR (NR) NR</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: family history of current or previous allergic symptoms, i.e. bronchial asthma, eczema, allergic food reactions, itching and running eyes and nose at exposure to pollen, pets or other known allergens.</p> <p>Exclusion Criteria: Allergy to soya or fish, treatment with anticoagulants or omega-3 fatty acid</p>	<p>Start time: Pregnant 25 weeks of gestation</p> <p>Duration: Pregnant 15 weeks (i.e., until delivery)</p> <p>Arm 1: Placebo Description soya bean oil Manufacturer Pharma Nord, Vejle, Denmark Active ingredients 58% linoleic acid (LA), 2.5 g/day Viability the antioxidant a-tocopherol (placebo: 36 mg/day) to assure the stability of the oil N-3 Composition. Dose nine capsules a day Blinding The mothers, as well as the staff handling clinical and laboratory follow-up, were blinded to group allocation, and the mothers were identified by their study number only. ALA 6%, 0.28 g/day</p>	<p>Outcome any eczema Follow-up time 2 years Arm 1 21/65 (32.31%) Arm 2 11/54 (20.37%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Follow-up article(s) ^{149, 167}	(100)	supplements.	Arm 2: w-3 group Description w-3 fatty acids Viability the antioxidant a-tocopherol (w-3 group: 28 mg/day) to assure the stability of the oil N-3 Composition DHA & EPA Dose nine capsules a day DHA 25% DHA, 1.1 g/day EPA 35% EPA, 1.6 g/day	
<p>Linnamaa et al., 2010⁸²</p> <p>Study name: NR</p> <p>Study dates: 2004-2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Finland</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Infants enrolled 314 Infants withdrawals 137 Infants completers 177</p> <p>Mother age: NR (NR) NR</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: All pregnant mothers <16 weeks of gestation</p> <p>Exclusion Criteria: Sick children and those born prematurely who required more intensive care (n=8)</p>	<p>Start time: Pregnant 8th to 16th weeks of pregnancy and then continued Infants when exclusive breastfeeding ended</p> <p>Duration: Pregnant until the end of the exclusive breastfeeding period Infants until 2 years of age</p> <p>Arm 1: Controls Description Olive oil Manufacturer Santagata Luigi s.r.l., Genova, Italia N-3 Composition. Dose 3 g/day for mothers, 1 mL/day for infants Blinding NR "double-blind" ALA 0 DHA 0 EPA 0 EPA-DHA 0 AA 0 Total N-3 0 Other dose 1 LA (18:2n-6): 9 weight% of total</p> <p>Arm 2: Intervention Description Blackcurrant seed oil Manufacturer Aromtech Ltd, Tornio, Finland N-3 Compositions shown in Table 1 Dose 3 g/day for mothers, 1 mL/day for infants ALA 14 weight% of total DHA 0 EPA 0 EPA-DHA 0 AA 0 Total N-3 17 weight% of total Other comment 1 SDA: 3 weight% of total</p>	<p>Outcome atopic dermatitis</p> <p>Follow-up time 12 months Arm 1 52/110 (47.27%) Arm 2 33/100 (33%)</p> <p>Follow-up time 24 months Arm 1 10/92 (11.11%) Arm 2 9/85 (11.11%)</p> <p>Follow-up time 3 months Arm 1 14/129 (11.11%) Arm 2 12/112 (11.11%)</p>
Noakes et al., 2012 ¹⁵⁰	Study Population: Healthy pregnant women	Inclusion Criteria: age 18–40 y; >19 wk	Start time: Pregnant 20 weeks of gestation	Outcome atopic dermatitis Follow-up time 6 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study name: SiPS</p> <p>Study dates: NR</p> <p>Study design: Trial randomized parallel</p> <p>Location: UK</p> <p>Funding source / conflict: Government, None</p>	<p>Pregnant enrolled 123 Pregnant withdrawals 37 Pregnant completers 86</p> <p>Pregnant age: Mean(SEM)(n):Control group -28.4 (0.6)(61); Salmon group- 29.5(0.5) (62) (NR) 18-40 years</p> <p>Race of Mother: NR (100)</p>	<p>gestation; healthy uncomplicated singleton pregnancy; infant at risk of atopy (one or more first-degree relatives of the infant affected by atopy, asthma or allergy by self-report); consumption of < 2 portions oily fish per month, excluding tinned tuna; and no use of fish-oil supplements currently or in the previous 3 months.</p> <p>Exclusion Criteria: age <18 or >40 y; <19 wk gestation; no first-degree relatives of the infant affected by atopy, asthma, or allergy; consumption of >2 portions oily fish per month, excluding tinned tuna; use of fish-oil supplements within the previous 3 mo; participation in another research study; known diabetes; presence of any autoimmune disease; learning disability; terminal illness; and mental health problems.</p>	<p>Duration: Pregnant until birth</p> <p>Arm 1: Control group Description Women in the control group (n = 61) were asked to continue their habitual diet Blinding Researchers responsible for assessing outcome measures (both laboratory and clinical) remained blinded to the groups Arm 2: Salmon group Description Women in the salmon group (n = 62) were asked to incorporate 2 portions of farmed salmon (150 g/portion) into their diet per week Active ingredients 30.5 g protein, 16.4 g fat, 4.1 mg alpha-tocopherol, 1.6 mg gamma-tocopherol, 6 micro-g vitamin A, 14 micro-g vitamin D3, and 43 micro-g Selenium Dose two 150-g portions per week DHA 1.16 g per portion EPA 0.57g per portion EPA-DHA 1.73 per portion Total N-3 3.56g per portion Other comment 1 Docosapentaenoic acid-0.35g</p>	<p>Arm 1 12/48 (25%) Arm 2 7/38 (18.42%)</p>

Table 21. Observational studies for Atopic dermatitis

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Wijga, et al., 2006¹⁵⁴</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 276 Pregnant withdrawals 11 Pregnant completers 265</p> <p>Infants enrolled 276 Infants withdrawals 11 Infants completers 265</p> <p>Pregnant age: 31.0 (3.9) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Mothers reporting at least 1 of the following: (a history of) asthma, current hay fever, current allergy for pets, or current allergy for house dust or house dust mite were defined as allergic, and mothers reporting that they had none of these were defined as nonallergic.</p> <p>Exclusion Criteria: NR</p>
<p>Newson, et al., 2004¹⁵⁵</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: UK</p> <p>Funding source / conflict: Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 4136</p> <p>Infants enrolled 4202</p> <p>Infant age: NR (NR) NR</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: Women were enrolled as early in pregnancy as possible on the basis of an expected date of delivery between April 1, 1991, and December 31, 1992, and place of residence within the 3 Bristol-based health districts of the former county of Avon, United Kingdom</p> <p>Exclusion Criteria: NR for enrollment. Exclusion for analysis: We excluded 722 children from the maternal fatty acid analyses and 216 children from the cord fatty acid analyses who were from multiple pregnancies or who were in small missing value categories for various confounders.</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Standl, et al., 2014¹⁵⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Germany</p> <p>Funding source / conflict: Government</p> <p>Follow-up article(s) supplemental materials</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 436 Infants completers 243</p> <p>Mother age: 32.7 (3.9) NR</p> <p>Infant age: NR (NR) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: Neonates displaying at least one of the following criteria: preterm birth (maturity <37 gestational weeks), low birth weight (<2,500 g), congenital malformation, symptomatic neonatal infection, antibiotic medication, hospitalization or intensive medical care during neonatal period. In addition, newborns from mothers with immune-related diseases (autoimmune disorders, diabetes, hepatitis B), on long-term medication or who abuse drugs and/or alcohol, and newborns from parents with a nationality other than German or who were not born in Germany, were excluded.</p>
<p>Thijs, et al., 2011¹⁵⁷</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 312 Pregnant completers 304</p> <p>Infants enrolled 312 Infants completers 304</p> <p>Pregnant age: 33.3 (3.9) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: availability of complete baseline data from the 34 weeks pregnancy questionnaire and availability of a breast milk sample.</p> <p>Exclusion Criteria: NR</p>
<p>Notenboom, et al., 2011¹⁵⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Infants enrolled 1275 Infants completers 1253</p> <p>Mother age: 32.6 (3.8)</p> <p>Race of Mother: White European (Dutch 96.3%)</p>	<p>Inclusion Criteria: A detailed description of the design has been provided elsewhere [12]... The present study population consists of participants recruited from January 2002 onwards who consented to biosampling. Maternal blood samples (n= 1374) were taken in the 34th–36th week of pregnancy and venous blood samples from their offspring at age 24 months (n= 815)</p> <p>Exclusion Criteria: Current multiple pregnancy n=9 Prematurity n=15 Perinatal infant death n=2 Down syndrome n=4 No response after birth n=51</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Nwaru, et al., 2012¹⁵⁹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Finland</p> <p>Funding source / conflict: Government, Multiple foundations and Societies</p>	<p>Study Population: NR</p> <p>Infants enrolled 2441</p> <p>Infant age: NR (NR) NR</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: Newborn infants with human leucocyte antigen (HLA)- conferred susceptibility to type 1 diabetes are recruited from three university hospitals in Finland...</p> <p>Exclusion Criteria: NR - check Ref 12</p>
<p>Saito, et al., 2010¹⁶⁰</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Japan</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant completers 771</p> <p>Infants completers 771</p> <p>Pregnant age: 29.9 (4.0)</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: Eligible pregnant women were those who lived in Neyagawa City, which is one of the 43 municipalities in Osaka Prefecture, a metropolis in Japan with a total population of approximately 8.8 million...In order to increase the sample size, pregnant women living in municipalities other than Neyagawa City were also recruited.</p> <p>Exclusion Criteria: Survey completed outside 3-5 month postpartum window</p>

Allergies

Key Points

- Among the three prenatal n-3 interventions and two follow-up studies, three found associations between maternal n-3 FA supplementation (DHA + EPA, varying doses) and lower risk of allergies (denoted by sensitization to egg allergen and positive skin prick test). However, in all but one study, these relationships were no longer observed or became marginal after adjusting for potential confounders or after long-term follow-up. Meta-analysis of three RCTs (n=949) with 12 month food allergy outcomes yielded a non-significant summary effect. A single trial with ALA supplementation also found no relationship.
- In three postnatal n-3 interventions and one follow-up study, there was no consistent association between infant n-3 FA supplementation (DHA or DHA+EPA, varying doses) and allergy outcomes.
- One biomarker study found associations between higher levels of DHA and lower incidence of IgE-associated disease as well as lower AA/EPA ratio with higher incidence of IgE-associated disease, although these findings were not consistent over time.
- There was no robust association between n-3 FA exposure (measured through maternal dietary intake or breast milk composition) and allergy outcomes among three prospective observational studies. The associations found in these studies lost significance after adjusting for multiple comparisons or after longer term follow-up. All three studies of n-3 FA biomarkers (in cord blood or maternal blood sample) and risk of allergy found no significant association.

The risk for allergies is an additional outcome of interest that was not included in the original review. A total of 10 eligible RCTs (composed of 7 original RCTs and 3 follow-up assessments) and 6 observational studies were included.

Randomized Controlled Trials

Prenatal interventions/exposures

Four RCTs^{48, 57, 82, 149} and 2 follow-up assessments^{53, 148} evaluated n-3 FA interventions given to the mother during the prenatal period. Two interventions were exclusively during the prenatal period with the mother stopping supplementation at birth.^{48, 53, 57} The two remaining trials with maternal supplementation started during pregnancy and continued into breastfeeding,^{82, 148, 149} with one of those trials also adding infant supplementation following breastfeeding.⁸² All of these trials except for one⁸² recruited pregnant women whose infants were at high risk for atopy (e.g., parent diagnosis of allergy, or sibling has diagnosed or suspected allergy). All studies tested DHA and DHA+EPA n-3 FAs except for a single RCT that evaluated ALA.⁸²

DHA, DHA + EPA vs. placebo

One RCT randomized 145 pregnant women in Sweden to daily n-3 (1.6g EPA + 1.1g DHA) or placebo (soy oil) supplementation from the 25th gestational week through the exclusive breastfeeding period (average 3-4 months). Period prevalence for the first 12 months of life was lower in adjusted analyses for all skin prick tests (OR 0.36; 95% CI 0.14, 0.95), egg skin prick test (OR 0.31, 95% CI 0.11-0.89), and food allergy (OR 0.09, 95% CI 0.01-0.74).¹⁴⁹ In a later

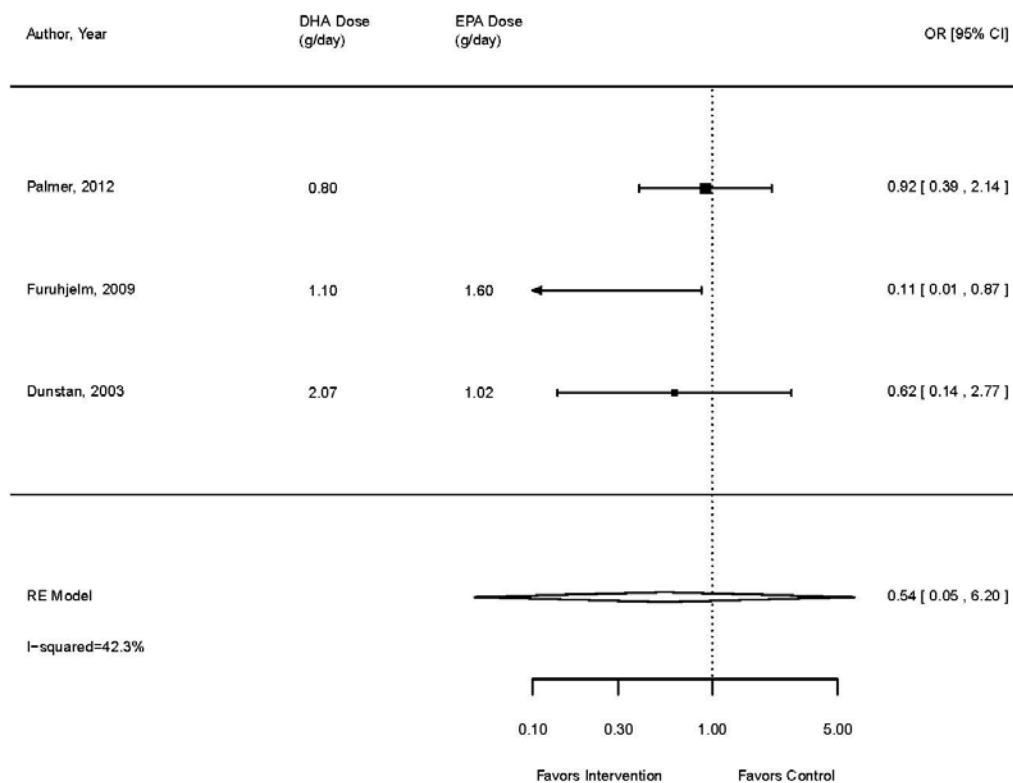
follow-up study at 24 months with 143 infants, marginal differences were observed in crude incidence and prevalence rates for food reactions between the treatment groups. In adjusted multiple regression models, risk of any positive skin prick test through 24 months was marginally but not statistically lower for the n-3 group (OR 0.43, 95% CI 0.17, 1.1; $p=0.06$).¹⁴⁸

Dunstan et al. (2003) randomized 98 pregnant, atopic Australian women to fish oil (3.7g n-3 PUFA, 56.0% DHA, 27.7% EPA) or olive oil (4g) daily from 20 weeks gestation until delivery.⁵⁷ A total of 83 mothers and their children completed the 12-month follow-up. The authors report that infants in the fish oil group were less likely to be sensitized to egg allergen (OR 0.34, 95% CI 0.11, 1.02; $p=0.055$). There were no significant differences in other clinical outcomes, including food allergy and anaphylaxis, between the fish oil and control groups.⁵⁷

In a subset of the Docosahexaenoic Acid (DHA) to Optimise Mother Infant Outcome (DOMInO) trial, 706 pregnant Australian women whose child was at high risk for genetic allergy were randomized to n-3 LCPUFA group (800 mg DHA + 100 mg EPA) or placebo group (vegetable oil) from 21 weeks gestation until delivery.^{48, 53} In a 1-year follow-up, no differences were seen between treatment groups for allergic disease with sensitization, allergic disease without sensitization, food allergy with sensitization, sensitization with/without allergic disease, or allergic disease without sensitization in analyses adjusted and unadjusted for study centre, parity, maternal history, and sex, although some relationships reached marginal significance.⁴⁸ The one exception was that the n-3 LCPUFA group were at lower risk for egg sensitization compared to the placebo group (RR 0.75; 95% CI 0.41, 0.93; $p=0.02$). In a longer follow-up, no differences were observed between treatment groups for allergic disease with sensitization, allergic disease without sensitization, food allergy with sensitization, allergic rhinitis with sensitization, sensitization during the first 3 years of life or at age 3 in analyses adjusted and unadjusted for study centre, parity, maternal history, and sex.⁵³

Meta-analysis of the three RCTs with a 12 month follow-up^{48, 57, 149} yielded a non-significant summary effect size for DHA supplementation and risk of food allergy (OR 0.54 95% CI 0.05, 6.2, $I^2=42.3\%$) (Figure 20).

Figure 20. Food Allergy – Intervention given to pregnant women, 12-month follow-up



ALA vs. placebo

One trial examined ALA supplementation during pregnancy, breastfeeding, and infancy.⁸² Specifically, Linnamaa et al. (2010) randomized 313 pregnant Finnish women (<16 weeks gestation) to blackcurrant seed oil (14% ALA by weight of 3g/d) or olive oil (placebo). The first dose was administered between the 8th to 16th week of pregnancy and continued during breastfeeding. Once the exclusive breastfeeding period was over, infants received 1 mL/day of supplemental oil until age 2 years. Total IgE antibodies were available for 136 infants at 3 and 12 months and 64 infants at 24 months; results from skin prick tests with egg were available for 238, 202, and 166 infants at 3, 12, and 25 months, respectively. No significant differences were observed between the intervention and placebo groups at any time point.

Postnatal interventions/exposures

Three RCTs^{112, 125, 152} and one follow-up study¹⁵¹ evaluated n-3 FA interventions during the postnatal period. One of the RCTs evaluated preterm infants¹¹² while the remaining two RCTs

assessed term infants who were at genetic risk for allergy.^{125, 152} All RCTs evaluated DHA or DHA+EPA n-3 FAs.

DHA, DHA + EPA vs. placebo

One RCT, which enrolled mothers of preterm infants, began the n-3 FA intervention during the postnatal breastfeeding period.¹¹² The DINO trial randomized 657 preterm Australian infants (<33 weeks gestation) to receive a high-DHA diet (~1% DHA and 0.6% AA) or standard DHA diet (~0.35% DHA and 0.6% AA) through breast milk or formula until their expected delivery date. Data from parent questionnaires on hay fever were available for 481 infants at 12 months and 603 infants at 18 months. In adjusted analyses, infants in the high-DHA diet group had lower risk of reported hay fever at 12 or 18 months (RR 0.41; 95% CI 0.18-0.91; p=0.03), but not at either time points separately (12 mo RR 0.41, 95% CI 0.15, 1.16; p=0.09; and 18 mo RR 0.75, 95% CI 0.28, 2.01; p=0.57). Data on special diet for food allergy were available for 480 infants at 12 months and 603 infants at 18 months. No differences were seen in food allergy at either time point (adjusted or unadjusted for gestational age at delivery and gender).¹¹²

In the Infant Fish Oil Supplementation Study (IFOS), 420 infants at high risk for atopy were randomized to daily fish oil capsules (0.280 g DHA + 0.110 g EPA) or placebo capsules (olive oil) from birth to 6 months. No significant overall difference was observed in the prevalence of any allergic disease, overall sensitization, specific sensitization, or food allergy at 12 months between the fish oil and placebo groups in both adjusted and unadjusted analyses.¹²⁵

One RCT on infant n-3 supplementation came from the Childhood Asthma Prevention Study (CAPS).^{151, 152} In CAPS, 616 pregnant women (<36 weeks gestation) whose child was at high risk for developing asthma were randomized into four groups, including two with a dietary component (500 g/d tuna fish oil supplement + canola-based oils and spreads or placebo supplement + polyunsaturated oils and margarines) from 6 months or the beginning of formula feeding if that occurred earlier than 6 months. In an 18-month follow-up with 543 infants (88% of the total sample size), geometric mean IgE concentrations did not differ between the diet intervention and control groups.¹⁵¹ In a 5-year follow-up with 516 children (84%), no significant differences were seen between the diet intervention and control groups for rhinitis (RR 1.42; 95% CI 0.97, 2.09), any atopy (RR 0.93, 95% CI 0.76, 1.13), inhalant atopy (RR 0.96, 95% CI 0.78, 1.18), house dust mite atopy (RR 1.04, 95% CI 0.81, 1.33), or IgE (ratio of means, 0.86, 95% CI 0.64, 1.16).¹⁵²

Biomarker Studies

One trial examined the association between biomarkers and allergy outcomes.¹⁴⁸ Results suggest that higher maternal (p for trend=0.001) plasma phospholipid DHA is significantly associated with lower incidence of IgE-associated disease at 12 months of age. Higher infant (p for trend=0.003) plasma phospholipid DHA was significantly associated with lower incidence of IgE-associated disease at 12 months of age. Infant plasma phospholipid DHA was not significantly associated with IgE-associated disease at 3 or 24 months of age. In addition, lower maternal plasma phospholipid AA/EPA ratio was associated with higher incidence of IgE-associated disease (p for trend=0.008). Lower quartiles of AA/EPA ratios in infant phospholipids at birth and at 3 months of age were associated with lower incidence of IgE-associated disease (p = NS for both, but p for trend = 0.01 and 0.03 respectively), but no significant relationship with infant phospholipids at 12 or at 24 months. At 12 and 24 months of age, AA/EPA ratios in infant phospholipids were also not significantly associated with IgE-associated disease.¹⁴⁸

Observational Studies

Six observational studies evaluated the association between some measure of n-3 FA exposure and risk of allergies.^{154, 156-159, 168}

All studies enrolled population of healthy infants except for one¹⁵⁹ which enrolled infants with human leucocyte antigen (HLA)-conferred susceptibility-hence high or moderate genetic risk - to type I diabetes. All the studies were prospective cohort studies. The exposures include dietary intake of n-3 FA,¹⁵⁹ breast milk FA,^{154, 157} and maternal biomarkers.^{156, 158, 168} Studies were published between 2004 and 2014.

Maternal n-3 FA Intake

A single study evaluated the association between maternal dietary n-3 FA intake and risk of allergies.¹⁵⁹

A 2012 study examined the association between maternal n-3 FA intake in a cohort of 2441 newborn infants born between 1997 and 2004 in Finland and risk of allergies after 5 years of follow-up. Enrolled infants had a history of human leucocyte antigen (HLA)-conferred susceptibility to type I diabetes. Maternal intake of n-3 FA was assessed using a validated FFQ. High maternal intakes of ALA (HR 0.73; 95 % CI 0.54, 0.98) were associated with a decreased risk of allergic rhinitis. Also, higher ratios of n-6: n-3 FA (HR 1.37; 95 % CI 1.07, 1.77) during pregnancy were associated with an increased risk of allergic rhinitis in the offspring by 5 years of age, adjusted for potential confounding variables. The results however lost their significance after adjustment for multiple comparisons.¹⁵⁹

n-3 FA Breastmilk Intake

Two studies examined the association between breastmilk n-3 fatty acids and the risk for allergies in infants.^{154, 157}

A 2006 study of 265 mother-infant pairs in Netherland found no relationship between breast milk n-3 fatty acid concentration (measured at 3 months postpartum) and sensitization (defined as specific IgE higher than 0.35 IU/mL to any of measured allergens) in children with maternal history of allergy at 4 years of age. However in children with no maternal history at 4 years of age, ALA and ALA/LA ratio were positively associated with sensitization ($p < 0.05$).¹⁵⁴

In a 2011 study of 310 mother-infant pairs in Netherlands, higher concentrations of breast milk n-3 fatty acid (EPA+DHA+DPA) were significantly associated with lower risk of allergic sensitization at 1 year of age (p for trend=0.029), adjusted for recruitment group, maternal age, maternal education, infant's gender, number of older siblings and their atopic history, parental atopic history, maternal smoking during pregnancy and/or smoking in presence of the infant, place of birth, season of breast milk collection, and other potential confounders). However, no significant associations were found at 2 years of age.¹⁵⁷

n-3 FA Biomarkers

Three studies examined the association between n-3 FA biomarkers and the risk of allergies.^{156, 158, 168}

In a 2011 study of 1275 children from the KOALA Birth Cohort Study who were followed for 6-7 years, no associations were found between maternal plasma phospholipid n-3 fatty acids measured at 34-36 weeks of pregnancy and allergic sensitization, allergic rhinoconjunctivitis, or high total IgE.¹⁵⁸

In a 2012 study of 1485 healthy mother-infant pairs from the Southampton Women's Survey in the UK who were followed for 6 years, no associations were found between maternal plasma phospholipid n-3 fatty acids measured at 34 weeks of gestation and risk of atopy (positive skin prick test defined as positive wheal ≥ 3 mm to a common allergen panel).¹⁶⁸

A 2014 study of 436 infants from the Munich LISA plus birth cohort study in Germany found no significant association between n-3 LC-PUFA or n-6/n-3 ratio in cord blood serum and hay fever or allergic rhinitis and aeroallergen sensitization at 6 and 10 years' follow-up.¹⁵⁶

Observational study subgroup analyses

A 2006 study of 265 mother-infant pairs in Netherland stratified its analysis by presence or absence of allergy in mothers. The study found no relationship between breast milk n-3 fatty acid concentration (measured at 3 months postpartum) and sensitization (defined as specific IgE higher than 0.35 IU/mL to any of measured allergens) in children with maternal history of allergy at 4 years of age. However in children of mothers with no allergy at 4 years of age, alpha-linolenic acid (18:3n-3) and ALA/LA ratio was positively associated with sensitization ($p < 0.05$).¹⁵⁴

Table 22. RCTs for Allergies

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Marks et al., 2006¹⁵²</p> <p>Study name: CAPS</p> <p>Study dates: 1997-2004</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 5 years</p> <p>Follow-up article(s)^{164, 165, 151, 166, 153}</p>	<p>Study Population: Pregnant women with allergies</p> <p>Pregnant enrolled 616 Pregnant withdrawals 100 Pregnant completers 516</p> <p>Infants completers 516</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: pregnant women whose unborn children were at increased risk of developing asthma because 1 or more parents or siblings had asthma or wheezing</p> <p>Exclusion Criteria: with a pet cat at home, strict vegetarians, women with a nonsingleton pregnancy, and infants born earlier than 36 weeks of gestation. Infants had birth weights less than 2.5 kg, significant congenital malformations, or other significant neonatal disease.</p>	<p>Start time: Infants from the time the child started bottle-feeding, or to solid foods from age 6 months</p> <p>Duration: NR</p> <p>Arm 1: Diet control Description polyunsaturated oils and spreads, containing 40% w6 FA, and sunola oil capsules Manufacturer Crisco-Meadow Lea Foods Inc, Sydney, Australia Blinding The approach to blinding participants and research staff is described in this article's Online Repository at www.jacionline.org.</p> <p>Arm 2: Active Description canola-based oils and spreads, which are low in n-6 fatty acids, and tuna oil capsules, which contain n-3 fatty acids.</p>	<p>Outcome any atopy (from skin prick test) Follow-up time 5 years Arm 1 108/249 (43.37%) Arm 2 109/267 (40.82%) Outcome rhinitis Follow-up time 5 years Arm 1 102/249 (40.96%) Arm 2 111/267 (41.57%)</p>
<p>Manley et al., 2011¹¹²</p> <p>Study name: DINO</p> <p>Study dates: 2001-2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations</p>	<p>Study Population: Preterm infants Breast-feeding women</p> <p>Infants enrolled 657 Infants completers 614</p> <p>Lactating age: Intervention: 29.9 (5.8) Placebo: 30.2 (5.4)</p> <p>Infant age: 4 days (median)</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: Infants born before 33 weeks' gestation, within 5 days of the infant commencing any enteral feedings.</p> <p>Exclusion Criteria: major congenital or chromosomal abnormalities, from a multiple birth in which not all live-born infants were eligible, enrolled in other trials of fatty acid supplementation, or mother with contraindication to fish oil</p>	<p>Start time: Infants Within 5 days (or less) of starting enteral feeding</p> <p>Duration: Infants NR</p> <p>Arm 1: Standard DHA diet Description Soy bean oil Manufacturer Clover Corporation Dose 6 capsules per day Maternal conditions Infant conditions Current smoker 25% during pregnancy Other maternal conditions 1arm_1_maternal_conditions_other1 Other maternal conditions 2 Birth by C-section: 69% Pre-term birth 100% Low birth weight 18.6% Arm 2: High DHA</p>	<p>Outcome hay fever Follow-up time 12 months Arm 1 13/249 (5.22%) Arm 2 5/232 (2.16%) Follow-up time 12 or 18 months Arm 1 21/244 (8.61%) Arm 2 8/231 (3.46%) Follow-up time 18 months Arm 1 10/311 (3.22%) Arm 2 7/292 (2.4%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Follow-up: 18 months see above Follow-up article(s) ^{111, 100, 113, 101, 114} ,			Description Tuna fish oil Manufacturer Clover Corporation Dose 6 500-mg DHA-rich tuna oil capsules per day Maternal conditions Infant conditions DHA DHA to achieve a breast milk concentration that was 1% of total fatty acids Current smoker 25% during pregnancy Other maternal conditions 1arm_2_maternal_conditions_other1 Other maternal conditions 2 Birth by c-section: 68.3% Other comment 1 If supplementary formula was required, infants were given a high- DHA preterm formula (approximately 1.0%DHAand 0.6% AA).	
Palmer et al., 2012 ⁴⁸ Study name: DOMInO Study dates: 2006-2009 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government, Manufacturer supplied product Follow-up: 9415 Follow-up article(s) ^{34, 49, 50, 51, 52, 53, 3} ,	Study Population: Pregnant women with allergies Pregnant enrolled 706 Pregnant withdrawals 25 Pregnant completers 681 Infants enrolled 706 Infants withdrawals 25 Infants completers 681 Pregnant age: Treatment: 29.6 Placebo: 29.5 (Treatment: 5.7 Placebo: 5.6) NR Race of Mother: NR (100)	Inclusion Criteria: Included if the unborn baby had a mother, father, or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) and they were enrolled from the Women's and Children's Hospital or Flinders Medical Centre in Adelaide. Exclusion Criteria: NR	Start time: Pregnant 21 weeks of gestation Infants 21 weeks of gestation Duration: Pregnant until delivery Infants till delivery Arm 1: Placebo Description 338 women assigned to control supplements-vegetable oil capsules Dose three 500 mg vegetable oil capsules daily Blinding All capsules were similar in size, shape, and colour. . Neither the women nor the research staff were aware of the treatment allocated. Arm 2: n-3 LCPUFA group Description 368 women assigned to fish oil concentrate Brand name Incromega 500 TG Manufacturer Croda Chemicals, East Yorkshire, UK Dose e three 500 mg capsules daily DHA 800mg EPA 100mg	Outcome food allergy with sensitization Follow-up time 1 year Arm 1 11/338 (3.25%) Arm 2 11/368 (2.99%)
Palmer et al., 2013 ⁵³ Study name: DOMInO Study dates: 2006-2009 (allergy follow-up to Domino study)	Study Population: NR Pregnant enrolled 706 Pregnant completers 638 Infants enrolled 706 Infants completers 638	Inclusion Criteria: Women whose infants had a parent or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema)	Start time: Pregnant <21 weeks gestation Duration: Pregnant to term Arm 1: Control Description vegetable oil Dose 3 500-mg vegetable oil capsules per day	Outcome allergic rhinitis Follow-up time 3 years Arm 1 20/338 (5.92%) Arm 2 18/368 (4.89%) Outcome food allergy Follow-up time 3 years Arm 1 14/338 (4.14%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Industry, Government, Some authors serve on scientific advisory boards for corporations</p> <p>Follow-up: 3 years 3170, 3069</p> <p>Follow-up article(s) ^{34, 48, 49, 50, 51, 52, 3}</p>	<p>Pregnant age: DHA: 28.9 Control: 28.9 (DHA: 5.7) Control: 5.6)</p> <p>Infant age: Birth</p> <p>Race of Mother: NR (100)</p>	<p>Exclusion Criteria: Already taking a prenatal supplement with DHA Fetus had a known major abnormality, Bleeding disorder in which tuna oil was contraindicated, Taking anticoagulant therapy A documented history of drug or alcohol abuse, Participating in another fatty acid trial, Unable to give written informed consent, or English was not the main language spoken at home</p>	<p>Blinding This was a double-blinded study; all capsules were similar in size, shape and colour</p> <p>Arm 2: Fish oil</p> <p>Brand name Incromega 500 TG, Manufacturer Croda Chemicals, East Yorkshire, England</p> <p>Dose 3 500-mg capsules per day</p> <p>DHA 800 mg per day</p> <p>EPA 100 mg per day</p>	<p>Arm 2 18/368 (4.89%)</p>
<p>Dunstan et al., 2003⁵⁷</p> <p>Study name: Dunstan</p> <p>Study dates: 1999-2001</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 1 year 4381,6647</p> <p>Follow-up article(s) ^{42, 56, 58, 59}</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 98 Pregnant withdrawals 15 Pregnant completers 83</p> <p>Pregnant age: NR (NR) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: All women had a history of physician-diagnosed allergic rhinitis and/or asthma and 1 or more positive skin prick tests to common allergens (house dust mite; grass pollens; molds; and cat, dog, and cockroach extracts)</p> <p>Exclusion Criteria: Women were ineligible for the study if they smoked; if they had other medical problems, complicated pregnancies, or seafood allergy; or if their normal dietary intake exceeded 2 meals of fish per week.</p>	<p>Start time: Pregnant 20 weeks of gestation</p> <p>Duration: Pregnant till delivery</p> <p>Arm 1: Placebo group</p> <p>Description 46 women allocated and received placebo-olive oil</p> <p>Manufacturer Pan Laboratories, Moorebank, NSW, Australia</p> <p>Active ingredients 66.6% n-9 oleic acid N-3 Composition.</p> <p>Dose 4 (1-g) capsules of olive oil per day</p> <p>Blinding Randomization and allocation of capsules occurred at a different center separate from the recruitment of participants. Capsules were administered to the participants by someone separate from those doing the allocation. The capsules in the 2 groups were image-matched.</p> <p>Total N-3 <1% n-3 PUFAs</p> <p>Arm 2: Fish oil group</p> <p>Description 52 women were randomized to receive fish oil</p> <p>Manufacturer Ocean Nutrition, Halifax, Nova Scotia, Canada</p> <p>Dose 4 (1g) fish oil capsules per day</p>	<p>Outcome food allergy</p> <p>Follow-up time 1 year</p> <p>Arm 1 5/43 (11.63%)</p> <p>Arm 2 3/40 (7.5%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			_x001E__x0007__x0005__x0015__x0013__x0007__x001E__x0013__x000F_ DHA 56.0% EPA 27.7% Total N-3 3.7 g	
<p>D'Vaz et al., 2012¹²⁵</p> <p>Study name: IFOS</p> <p>Study dates: 2005-2009</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, None, Manufacturer supplied product</p> <p>Follow-up article(s) ¹²⁴, Protocol ID 5460</p>	<p>Study Population: Pregnant women with allergies</p> <p>Infants enrolled 420 Infants completers 323</p> <p>Pregnant age: Placebo: 33.2 Fish Oil: 32.5 (Placebo: 4.2 Fish Oil: 4.8)</p> <p>Infant age: Term (39.3 weeks gestation)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Maternal: Pregnant History of doctor diagnosed asthma or allergic rhinitis Skin prick positive to at least one allergen</p> <p>Exclusion Criteria: Maternal: Smoking Auto-immune disease Pre-existing medical conditions other than asthma High-risk pregnancy Seafood allergy Fish eaten more than three times per week Fish oil supplementation already taken (in excess of 1000 mg per day) Exclusion from data analysis criteria due to protocol deviations: Pre-term delivery (gestation <36 weeks) Infant with congenital abnormalities or significant disease not related to intervention</p>	<p>Start time: Infants Birth</p> <p>Duration: Infants 6 months</p> <p>Arm 1: Placebo Description Olive oil Manufacturer Ocean Nutrition, Ltd Dose 650 mg olive oil Blinding Randomization was completed by external staff via computer software using an unpredictable allocation sequence, stratified according to maternal and paternal atopic history and parity. Mothers and study personnel were unaware of the group allocation. Maternal conditions Maternal allergies 100 Arm 2: Fish oil group Manufacturer Ocean Nutrition Ltd. Purity Data fatty acid composition remained unchanged over the study period Dose 1 capsule contents, to be administered orally, prior to feeding in the morning Maternal conditions DHA 280 mg EPA 110 mg Maternal allergies 100</p>	<p>Outcome allergic disease (any of ige mediated food allergy, eczema or asthma) Follow-up time 12 months Arm 1 66/167 (39.52%) Arm 2 59/156 (37.82%) Outcome food allergy Follow-up time 12 months Arm 1 25/167 (14.97%) Arm 2 19/156 (12.18%)</p>
<p>Furuhjelm et al., 2009¹⁴⁹</p> <p>Study name: NR</p> <p>Study dates: 2003-2006</p> <p>Study design: Trial randomized parallel</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117</p>	<p>Inclusion Criteria: a family history of past of current allergic symptoms in at least one parent or older child.</p> <p>Exclusion Criteria: Mothers with an allergy</p>	<p>Start time: Pregnant 25 weeks of gestation</p> <p>Duration: Pregnant 15 weeks (i.e., until delivery)</p> <p>Arm 1: Placebo Description 75 women received soy oil as placebo Manufacturer Pharma Nord Active ingredients w-6 PUFA LA (58%, 2.5 g/day), a</p>	<p>Outcome Food Allergy Follow-up time 12 months Arm 1 10/65 (15.38%) Arm 2 1/52 (1.92%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Location: Sweden</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 1 year 303</p> <p>Follow-up article(s) ^{148, 167}</p>	<p>Infants enrolled 145 Infants withdrawals 28 Infants completers 117</p> <p>Mother age: Intervention: 31.1 years (at delivery) Placebo: 31.7 years (at delivery) (Intervention: 4.1 years (at delivery) Placebo: 3.9 years (at delivery)) NR</p> <p>Race of Mother: NR (100)</p>	<p>to soy or fish or undergoing treatment with anticoagulants or commercial w-3 fatty acid supplements</p>	<p>small amount (6%, 0.28 g/day) of the w-3 PUFA LNA and 36 mg α-tocopherol</p> <p>Viability α-tocopherol was given as an antioxidant, a necessary ingredient according to the standard procedure of the manufacturer to assure the durability of the oil.</p> <p>N-3 Composition.</p> <p>Dose nine soy oil capsules a day</p> <p>N-6 N-3 9</p> <p>Arm 2: w3 group</p> <p>Description 70 women are randomized into this group</p> <p>Brand name Bio Marin capsules</p> <p>Manufacturer Pharma Nord, Vejle, Denmark</p> <p>Active ingredients 23 mg α-tocopherol</p> <p>Viability α-tocopherol was given as an antioxidant, a necessary ingredient according to the standard procedure of the manufacturer to assure the durability of the oil.</p> <p>Dose nine 500-mg capsules, once daily</p> <p>DHA 1.1g</p> <p>EPA 1.6g</p> <p>N-6 N-3 <0.1</p>	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Furuhjelm et al., 2011¹⁴⁸</p> <p>Study name: NR</p> <p>Study dates: 2003-2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: Sweden</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 2 years 4378</p> <p>Follow-up article(s)^{149, 167}</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117</p> <p>Infants enrolled 145 Infants withdrawals 28 Infants completers 117</p> <p>Pregnant age: NR (NR) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: family history of current or previous allergic symptoms, i.e. bronchial asthma, eczema, allergic food reactions, itching and running eyes and nose at exposure to pollen, pets or other known allergens.</p> <p>Exclusion Criteria: Allergy to soya or fish, treatment with anticoagulants or omega-3 fatty acid supplements.</p>	<p>Start time: Pregnant 25 weeks of gestation</p> <p>Duration: Pregnant 15 weeks (i.e., until delivery)</p> <p>Arm 1: Placebo Description soya bean oil Manufacturer Pharma Nord, Vejle, Denmark Active ingredients 58% linoleic acid (LA), 2.5 g/day Viability the antioxidant a-tocopherol (placebo: 36 mg/day) to assure the stability of the oil N-3 Composition. Dose nine capsules a day Blinding The mothers, as well as the staff handling clinical and laboratory follow-up, were blinded to group allocation, and the mothers were identified by their study number only. ALA 6%, 0.28 g/day Arm 2: w-3 group Description w-3 fatty acids Viability the antioxidant a-tocopherol (w-3 group: 28 mg/day) to assure the stability of the oil N-3 CompositionDHA & EPA Dose nine capsules a day DHA 25% DHA, 1.1 g/day EPA 35% EPA, 1.6 g/day</p>	<p>Outcome any food reactions</p> <p>Follow-up time 2 years Arm 2 6/54 (11.11%) Follow-up time 2.5 years Arm 1 16/65 (24.62%)</p>
<p>Linnamaa et al., 2010⁸²</p> <p>Study name: NR</p> <p>Study dates: 2004-2008</p> <p>Study design: Trial randomized parallel</p> <p>Location: Finland</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Infants enrolled 314 Infants withdrawals 137 Infants completers 177</p> <p>Mother age: NR (NR) NR</p> <p>Race of Mother: NR (NR)</p>	<p>Inclusion Criteria: All pregnant mothers <16 weeks of gestation</p> <p>Exclusion Criteria: Sick children and those born prematurely who required more intensive care (n=8)</p>	<p>Start time: Pregnant 8th to 16th weeks of pregnancy and then continued Infants when exclusive breastfeeding ended</p> <p>Duration: Pregnant until the end of the exclusive breastfeeding period Infants until 2 years of age</p> <p>Arm 1: Controls Description Olive oil Manufacturer Santagata Luigi s.r.l., Genova, Italia N-3 Composition. Dose 3 g/day for mothers, 1 mL/day for infants Blinding NR "double-blind" ALA 0 DHA 0 EPA 0 EPA-DHA 0</p>	<p>Outcome positive egg skin test</p> <p>Follow-up time 12 months Arm 1 18/104 (17.31%) Arm 2 14/98 (14.29%) Follow-up time 24 months Arm 1 7/87 (8.05%) Arm 2 4/79 (5.06%) Follow-up time 3 months Arm 1 1/126 (0.79%) Arm 2 1/112 (0.89%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			AA 0 Total N-3 0 Other dose 1 LA (18:2n-6): 9 weight% of total Arm 2: Intervention Description Blackcurrant seed oil Manufacturer Aromtech Ltd, Tornio, Finland N-3 Composition shown in Table 1 Dose 3 g/day for mothers, 1 mL/day for infants ALA 14 weight% of total DHA 0 EPA 0 EPA-DHA 0 AA 0 Total N-3 17 weight% of total Other comment 1 SDA: 3 weight% of total	

Table 23. Observational studies for Allergies

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Wijga, et al., 2006¹⁵⁴</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 276 Pregnant withdrawals 11 Pregnant completers 265</p> <p>Infants enrolled 276 Infants withdrawals 11 Infants completers 265</p> <p>Pregnant age: 31.0 (3.9) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Mothers reporting at least 1 of the following: (a history of) asthma, current hay fever, current allergy for pets, or current allergy for house dust or house dust mite were defined as allergic, and mothers reporting that they had none of these were defined as nonallergic.</p> <p>Exclusion Criteria: NR</p>
<p>Newson, et al., 2004¹⁵⁵</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: UK</p> <p>Funding source / conflict: Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 4136</p> <p>Infants enrolled 4202</p> <p>Infant age: NR (NR) NR</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: Women were enrolled as early in pregnancy as possible on the basis of an expected date of delivery between April 1, 1991, and December 31, 1992, and place of residence within the 3 Bristol-based health districts of the former county of Avon, United Kingdom</p> <p>Exclusion Criteria: NR for enrollment. Exclusion for analysis: We excluded 722 children from the maternal fatty acid analyses and 216 children from the cord fatty acid analyses who were from multiple pregnancies or who were in small missing value categories for various confounders.</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Standl, et al., 2014¹⁵⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Germany</p> <p>Funding source / conflict: Government</p> <p>Follow-up article(s) supplemental materials</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 436 Infants completers 243</p> <p>Mother age: 32.7 (3.9) NR</p> <p>Infant age: NR (NR) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: Neonates displaying at least one of the following criteria: preterm birth (maturity <37 gestational weeks), low birth weight (<2,500 g), congenital malformation, symptomatic neonatal infection, antibiotic medication, hospitalization or intensive medical care during neonatal period. In addition, newborns from mothers with immune-related diseases (autoimmune disorders, diabetes, hepatitis B), on long-term medication or who abuse drugs and/or alcohol, and newborns from parents with a nationality other than German or who were not born in Germany, were excluded.</p>
<p>Lumia, et al., 2011¹⁶⁹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: NR</p> <p>Location: Finland</p> <p>Funding source / conflict: Industry, Government, Multiple foundations and Societies, None</p> <p>Follow-up: Baseline article not included</p>	<p>Study Population: NR</p> <p>Infants enrolled 2680 Infants completers 2679</p> <p>Pregnant age: 14.8% <25 years at birth 35.4% 25-29 years 30.4% 30-34 years 19.5% ≥35 years</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: infants at three university hospitals in Finland (Turku, Tampere and Oulu) whose cord blood was screened for HLA-conferred genetic susceptibility to type 1 diabetes (HLA-DQB1) and were found to have high or moderate genetic risk of type 1 diabetes</p> <p>Exclusion Criteria: Severe congenital malformations or diseases, parents of non-Caucasian origin or parents who did not have a working knowledge of Finnish, Swedish or English</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Morales, et al., 2012¹⁶³</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Spain</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 622 Pregnant completers 580</p> <p>Infants enrolled 622 Infants completers 580</p> <p>Mother age: 31.6 (4.2)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: to be resident in the study area, to be at least 16 years old, to have a singleton pregnancy, to not have followed any programme of assisted reproduction, to wish to deliver in the reference hospital, and to have no communication problems</p> <p>Exclusion Criteria: NR</p>
<p>Thijs, et al., 2011¹⁵⁷</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 312 Pregnant completers 304</p> <p>Infants enrolled 312 Infants completers 304</p> <p>Pregnant age: 33.3 (3.9) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: availability of complete baseline data from the 34 weeks pregnancy questionnaire and availability of a breast milk sample.</p> <p>Exclusion Criteria: NR</p>
<p>Miyake, et al., 2009¹⁶¹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Japan</p> <p>Funding source / conflict: Government, None</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 1,002 Pregnant completers 763</p> <p>Infants enrolled 1,002 Infants completers 763</p> <p>Pregnant age: 30.0 (4.0)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: pregnant women living in Neyagawa City, Osaka Prefecture or the surrounding cities</p> <p>Exclusion Criteria: Not reported</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Miyake, et al., 2013¹⁶²</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Japan</p> <p>Funding source / conflict: Industry, Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 1757 Pregnant completers 1354</p> <p>Infants enrolled 1757 Infants completers 1354</p> <p>Pregnant age: 31.5 (4.1)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Women living in one of 7 prefectures on Kyushu Island who became pregnant from 2007-2008</p> <p>Exclusion Criteria: Failure to complete the study surveys</p>
<p>Notenboom, et al., 2011¹⁵⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Infants enrolled 1275 Infants completers 1253</p> <p>Mother age: 32.6 (3.8)</p> <p>Race of Mother: White European (Dutch 96.3%)</p>	<p>Inclusion Criteria: A detailed description of the design has been provided elsewhere [12]... The present study population consists of participants recruited from January 2002 onwards who consented to biosampling. Maternal blood samples (n= 1374) were taken in the 34th–36th week of pregnancy and venous blood samples from their offspring at age 24 months (n= 815)</p> <p>Exclusion Criteria: Current multiple pregnancy n=9 Prematurity n=15 Perinatal infant death n=2 Down syndrome n=4 No response after birth n=51</p>
<p>Nwaru, et al., 2012¹⁵⁹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Finland</p> <p>Funding source / conflict: Government, Multiple foundations and Societies</p>	<p>Study Population: NR</p> <p>Infants enrolled 2441</p> <p>Infant age: NR (NR) NR</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: Newborn infants with human leucocyte antigen (HLA)- conferred susceptibility to type 1 diabetes are recruited from three university hospitals in Finland...</p> <p>Exclusion Criteria: NR - check Ref 12</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Saito, et al., 2010¹⁶⁰</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Japan</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant completers 771</p> <p>Infants completers 771</p> <p>Pregnant age: 29.9 (4.0)</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: Eligible pregnant women were those who lived in Neyagawa City, which is one of the 43 municipalities in Osaka Prefecture, a metropolis in Japan with a total population of approximately 8.8 million...In order to increase the sample size, pregnant women living in municipalities other than Neyagawa City were also recruited.</p> <p>Exclusion Criteria: Survey completed outside 3-5 month postpartum window</p>
<p>Pike, et al., 2012¹⁶⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: UK</p> <p>Funding source / conflict: Government, Some authors serve on scientific advisory boards for corporations</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 1485</p> <p>Infants enrolled 1485 Infants completers 865</p> <p>Pregnant age: 30.4 (3.8)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: mothers and children in the Southampton Women's Survey</p> <p>Exclusion Criteria: Infants born ≥ 35 weeks' gestation were excluded to avoid abnormal lung development associated with prematurity</p>

Respiratory Illness (Including Asthma)

Key Points

- In seven prenatal n-3 interventions and one follow-up study, there was no robust association between maternal n-3 FA supplementation (DHA + EPA, varying doses) and respiratory illness. Six studies found no significant association with respiratory outcomes, although one study found asthma less likely in the treatment group after 16 years and another found lower risk of respiratory symptoms at 18 months, though not at earlier timepoints. In addition, meta-analysis of three of the RCTs (n=1315) with 12 month follow-up of wheeze outcomes yielded a non-significant summary effect.
- In three postnatal n-3 interventions and three follow-up studies, there was no significant association between infant n-3 FA supplementation (DHA or DHA+EPA, varying doses) and respiratory outcomes. Only a single study found a lower prevalence of wheeze at 18 months in the treatment group; however this finding no longer remained at the 3 or 5 year follow-up. Pooled analysis of the three RCTs (n=1693) with 18 month follow-up asthma outcomes yielded a non-significant summary effect.
- One biomarker study found higher levels of DHA and DHA + DPA + EPA at 6 months were associated with reduced risk of recurrent wheeze in the first 12 months.
- Five of six prospective observational studies found an inverse association between n-3 FA (measured through maternal dietary intake or breast milk composition) and risk of respiratory outcomes such as wheeze and asthma. The n-3 FA exposures in these studies ranged from ALA, DHA, EPA, EPA+DHA, total n-3 PUFA, and n-3/n-6 LCPUFA. Three of four prospective observational studies of n-3 FA biomarkers (in cord blood or maternal blood sample) found no relationship between n-3 FA biomarkers and risk of respiratory illness, with only one study reporting higher maternal EPA, DHA, and total n-3 FAs being associated with reduced risk of non-atopic persistent/late wheeze.

Description of Included Studies

This outcome is an additional outcome of interest that was not included in the original review. A total of 14 eligible studies (comprising of 12 RCTS and 2 follow-up studies) and 9 observational studies were included.

Prenatal maternal interventions/exposures

Randomized Controlled Trials

Eight studies (7 RCTs and 1 follow-up study) evaluated n-3 FA interventions given to the mother during the prenatal period.^{48, 53, 57, 72, 148, 150, 170, 171} All interventions were exclusively during the prenatal period with the mother stopping supplementation at birth, except for one that continued into breastfeeding.¹⁴⁸ Most of the trials recruited pregnant women whose infants were at high risk for atopy (e.g., parent diagnosis of allergy, or sibling with diagnosed or suspected allergy), except for three that recruited healthy pregnant women.^{72, 170, 171} All the studies tested DHA and DHA+EPA n-3 FAs versus placebo.

DHA, DHA + EPA vs. placebo

Olsen et al. (2008), followed up with a population-based sample of 533 pregnant women in Denmark randomized to 2.7g marine n-3 PUFA, olive oil, or no oil daily from 30 weeks until term.¹⁷⁰ Medical records were available for 528 children for a 16-year follow-up. The fish oil group was less likely to have occurrences of asthma (HR 0.37; 95% CI 0.15, 0.92) and allergic asthma (HR 0.13; 95% CI 0.03, 0.60) compared to the olive oil group.

Dunstan et al. (2003) randomized 98 pregnant, atopic Australian women to fish oil (3.7g n-3 PUFA, 56.0% DHA, 27.7% EPA) or olive oil (4g) daily from 20 weeks gestation until delivery.⁵⁷ A total of 83 mothers and their children completed the 12-month follow-up. No significant differences were seen in respiratory clinical outcomes, including recurrent wheeze, persistent cough, or diagnosed asthma, between the fish oil and control groups.⁵⁷

In the Salmon in Pregnancy Study (SiPS), 123 pregnant women in the UK were randomized to the salmon group (300g salmon / week) or control group (no changes in diet) from 20 weeks gestation until delivery.¹⁵⁰ Clinical outcomes were available for 86 infants at 6 months. No differences were seen in the incidence of wheeze, bronchiolitis, or chest infections between the salmon and control groups.¹⁵⁰

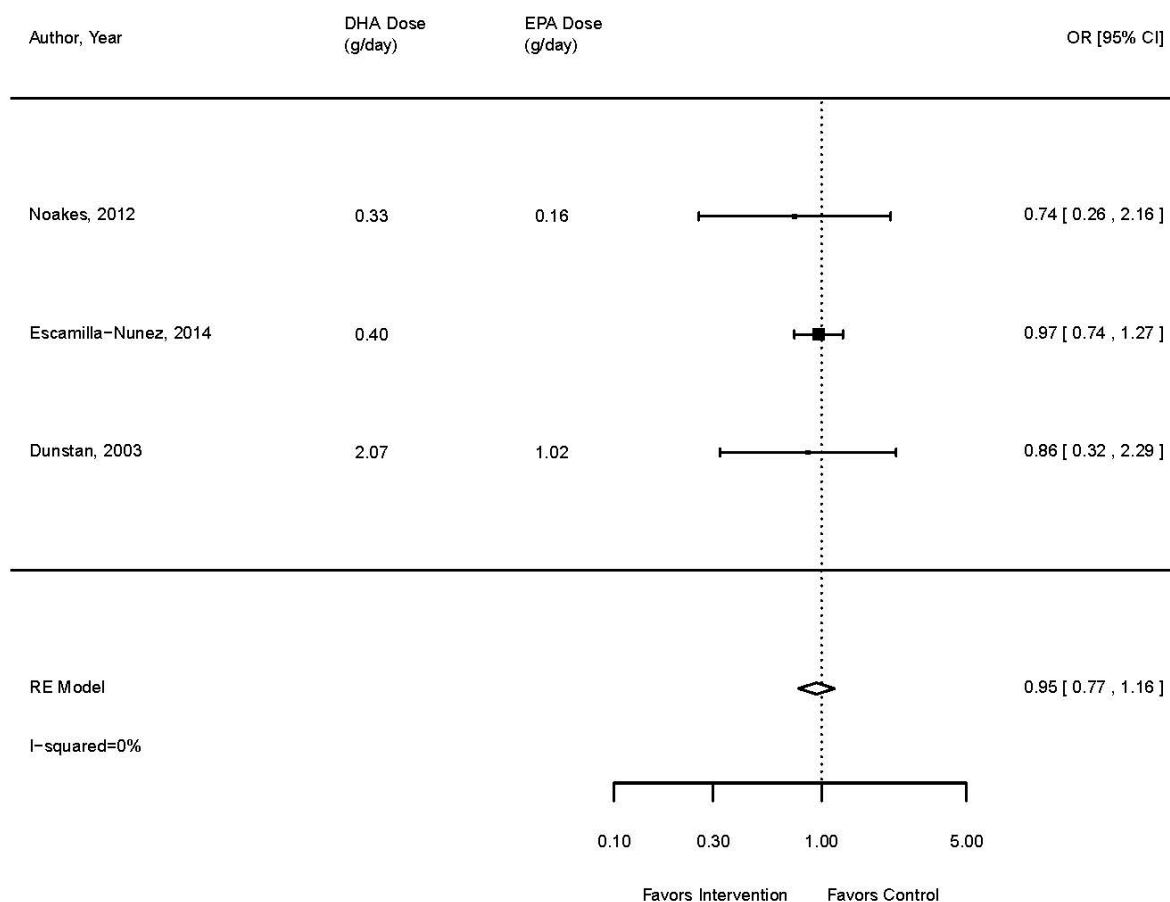
Another study randomized 1,094 pregnant women in Mexico to n-3 supplementation (400 mg DHA) or placebo (corn and soy oil) daily from mid-pregnancy (18-22 weeks gestation) until delivery.⁷² A total of 973 women completed the treatment. In crude analyses of respiratory symptoms up to age 18 months, DHA supplementation was associated with lower risk of three respiratory symptoms – “phlegm with congestion and/or nasal discharge,” fever with phlegm and congestion and/or nasal discharge,” and “wheezing with fever” (IRR 0.74; 95% CI 0.63, 0.87, IRR 0.52; 95% CI 0.38, 0.70, and IRR 0.43, 95% CI 0.21, 0.83, respectively). The authors reported significant interactions between the treatment group and the mother’s atopic status on a number of respiratory symptoms, indicating a greater protective effect of DHA supplementation in children of atopic mothers. An earlier study of the same cohort examined morbidity data for 849, 834, and 834 infants at 1, 3 and 6 months, respectively.¹⁷¹ The DHA group and placebo groups showed no differences at 1, 3, or 6 months for cough, wheezing, or difficulty breathing. The authors reported lower occurrence of cold (defined as any of the following: cough, phlegm, nasal congestion, nasal secretion) in the DHA group compared to the placebo group at 1 and 3 months (37.6% vs 44.6%; $P < .05$; and 37.8 vs 44.1; $P > .05$, respectively).

In a subset of the Docosahexaenoic Acid (DHA) to Optimise Mother Infant Outcome (DOMInO) trial, 706 pregnant Australian women whose child was at high familial risk for allergy were randomized to n-3 LCPUFA group (800 mg DHA + 100 mg EPA) or placebo group (vegetable oil) from 21 weeks gestation until delivery.^{48, 53} A 1-year follow-up was completed with 706 infants, but outcomes for respiratory manifestations did not differ between treatment groups.⁴⁸ Asthma with sensitization was rare during the first 3 years of life (6% (SD 1.8) in the n-3 LCPUFA group and 5 (SD 1.6)% in the placebo group with no differences between treatment groups (Fisher’s exact, $p=1.00$).⁵³

One RCT randomized 145 pregnant women in Sweden to daily n-3 (1.6g EPA + 1.1g DHA) or placebo (soy oil) supplementation from the 25th gestational week through the exclusive breastfeeding period (average 3-4 months). In a follow-up study with 143 infants, there were no differences in cumulative asthma (with and without sensitization) through 24 months or current asthma (with and without sensitization) at 24 months between the treatment groups.¹⁴⁸

Meta-analysis of three RCTs with a 12 month follow-up^{57, 150, 171} yielded a non-significant summary effect size for DHA supplementation and risk of wheeze (OR 0.95 95% CI 0.77, 1.16, $I^2=0\%$) (Figure 21).

Figure 21. Wheeze – Intervention given to pregnant women, 12-month follow-up



Postnatal maternal interventions/exposures

Four RCTs^{112, 114, 125, 151} and two follow-up studies^{152, 153} evaluated n-3 FA interventions during the postnatal period. One of the RCTs evaluated preterm infants¹¹⁴ while the remaining RCTs assessed term infants who were at genetic risk for allergy. All RCTs evaluated DHA and DHA+EPA n-3 FAs.

DHA, DHA+AA, or DHA + EPA vs. placebo

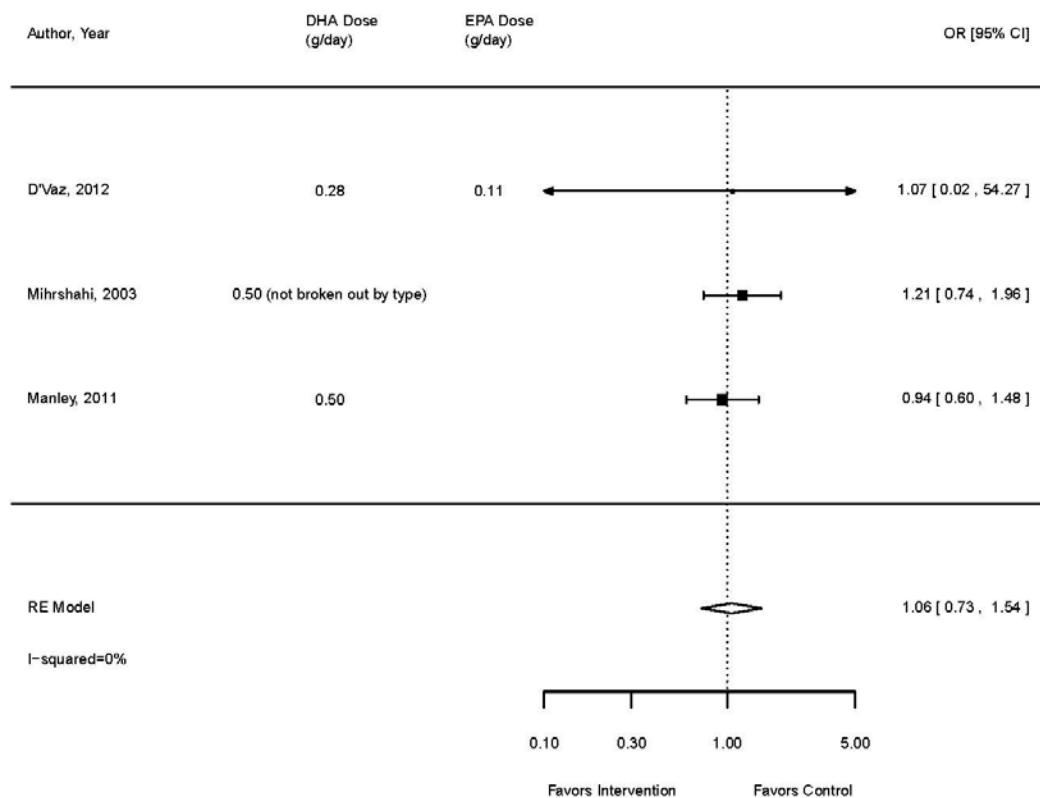
The DINO trial began the n-3 FA intervention during the postnatal breastfeeding period.¹¹²
¹¹⁴ The DINO trial randomized 657 preterm Australian infants (<33 weeks gestation) to receive a high-DHA diet (~1% DHA and 0.6% AA) or standard DHA diet (~0.35% DHA and 0.6% AA) through breast milk or formula until their expected delivery date. Data on asthma from a parent questionnaire were available for 481 infants at 12 months and 603 infants at 18 months. No differences were seen in asthma at either time point (adjusted or unadjusted for gestational age at delivery and gender).¹¹² Data on re-hospitalization were available for 648, 626, 615 and 611 at term, 4, 12 and 18 months' corrected age, respectively. There were no significant differences between the high-DHA and standard DHA groups in prevalence of any hospitalisation or the mean number of admissions for lower respiratory tract conditions such as wheezing and asthma, after 18 months.¹¹⁴

In the Infant Fish Oil Supplementation Study (IFOS), 420 infants at high risk for atopy were randomized to daily fish oil capsules (280 mg DHA + 110 mg EPA) or placebo capsules (olive oil) from birth to 6 months. There was no significant overall difference in prevalence of asthma at 12 months between the fish oil and placebo groups in unadjusted and adjusted analyses. Similarly, there were no differences in wheeze or persistent coughing at 6 or 12 months.¹²⁵

Three publications on infant n-3 supplementation came from the Childhood Asthma Prevention Study (CAPS).¹⁵¹⁻¹⁵³ In CAPS, 616 pregnant women (<36 weeks gestation) whose child was at high risk for developing asthma were randomized into 4 groups, including 2 with a dietary component (500 mg tuna fish oil supplement + canola-based oils and spreads or placebo supplement + polyunsaturated oils and margarines) from 6 months. In an 18-month follow-up with 543 infants (88% of the total sample size), the prevalence of wheeze was 9.8 percentage points lower and the prevalence of wheeze lasting longer than 1 week was 7.8 percentage points lower in the diet intervention group compared to the control group ($p=0.02$ and $p=0.04$, respectively).¹⁵¹ In a 3-year follow-up with 526 infants, no between-group differences were observed in the prevalence of asthma or wheeze, although mild cough was reduced by 7.1% and moderate cough by 4.1% in the diet group ($p=0.03$), with a larger reduction of 10.0% (95% CI 3.7, 16.4) in atopic cough when stratified by atopy.¹⁵³ In a 5-year follow-up with 516 children (84%), there were no significant differences between the diet intervention and control groups for probable current asthma (RR=1.13; 95% CI 0.82, 1.57) or cough without cold (RR=1.42, 95% CI 0.97, 2.09).¹⁵²

Meta-analysis of three RCTs with an 18 month follow-up^{112, 125, 151} yielded a non-significant summary effect size for DHA supplementation and risk of asthma (OR [95% CI]=1.06CI[0.73,1.54], $I^2=0\%$) (Figure 22).

Figure 22. Asthma – Intervention given to infants, 18-month follow-up



Biomarker Studies

A single RCT examined associations between biomarkers and respiratory outcomes. Results suggest that elevated plasma levels of DHA ($P = .027$) and total n-3 PUFA (EPA + docosapentaenoic acid [DPA] + DHA) at 6 months were associated with a reduced risk of recurrent wheeze in the first 12 months of life ($P = .028$).¹²⁵

Observational Studies

Nine observational studies evaluated the association between some measure of n-3 FA exposure and risk of respiratory illnesses.^{154-156, 158, 161-163, 168, 169}

All studies enrolled populations of healthy infants except for one¹⁶⁹ that enrolled infants who had high or moderate genetic risk of type I diabetes. All the studies were prospective cohort studies. The exposures include dietary intake of n-3 FA,^{161, 162, 169} breast milk FA,^{154, 163} and maternal biomarkers.^{155, 156, 158, 168} Included studies were published between 2004 and 2014.

n-3 FA Intake

We identified three studies that evaluated the association between dietary n-3 FA intake and risk of respiratory illness.^{161, 162, 169}

Lumia et al 2011 in their analysis of 2679 infant-mother pairs from the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study examined the association between maternal dietary intake during the 8th month of pregnancy (assessed by a validated 181-item FFQ) and risk of asthma in offspring at 5 years of age. Enrolled infants had a high to moderate risk of type I diabetes. Low maternal intakes of alpha-linolenic acid [lowest quarter vs. midhalf HR 1.70 (95% CI 1.14–2.53)] and total n-3-polyunsaturated fatty acids (PUFA) [HR 1.66 (95% CI 1.11–2.48)] during pregnancy were associated with an increased risk of asthma in the offspring, while a low intake of arachidonic acid [HR 0.52 (95% CI 0.32–0.84)] were associated with a decreased risk of asthma after adjusting for potential confounders. Also adjusting for Vitamin D intake did not change the results.¹⁶⁹

In a 2009 study of 763 healthy mother-infant pairs from the Osaka Maternal and Child Health Study in Japan, higher maternal intake of alpha-linolenic acid and docosahexaenoic acid during pregnancy was independently associated with a reduced risk of wheeze in the offspring (adjusted odds ratios (ORs) between extreme quartiles 0.52 (95% CI 0.28 to 0.97) and 0.37 (95% CI 0.15 to 0.91), respectively).¹⁶¹ Maternal dietary intake was assessed with a validated diet history questionnaire during pregnancy while wheeze was assessed by maternal report based on the International Study of Asthma and Allergies in Childhood for offspring at 16-24 months postpartum.

Also in a 2013 study of 1,354 healthy mother-infant pairs from the Kyushu Okinawa Maternal and Child Health Study (KOMCHS) in Japan, higher maternal intake of EPA (p for trend = 0.02) and EPA plus DHA (p for trend = 0.02) during pregnancy were associated with a reduced risk of wheeze in the offspring.¹⁶² Maternal dietary intake was assessed with a dietary history questionnaire during pregnancy while infantile wheeze was assessed by parental report based on the International Study of Asthma and Allergies in Childhood for offspring at 23-29 months postpartum.

n-3 FA Breastmilk Intake

Two additional studies examined the association between breastmilk n-3 fatty acids and the risk of respiratory illness.^{154, 163}

A 2006 study of 265 mother-infant pairs in Netherland found an inverse association between breast milk DHA concentration (measured at 3 months postpartum) and n-3/ n-6 LCPFA ratio with risk of asthma in children of mothers with allergy at 4 years of age (p<0.05).¹⁵⁴

A 2012 study of 580 infants in Spain found no significant association between colostrum n-3 LC-PUFA and risk of wheeze and lower respiratory tract infection during the first 14 months of life.¹⁶³ Colostrum was collected only for a random subsample (n=352) with n-3 LC-PUFA values imputed for the rest of the sample, however no differences were found in analyses with the colostrum subsample only.

n-3 FA Biomarkers

Four studies examined the association between n-3 FA biomarkers and the risk of respiratory illness.^{155, 156, 158, 168}

A 2004 study of 1238 mother-infant pairs conducted in the UK found a positive association between the ratio of linoleic acid: alpha-linolenic acid in cord blood and later-onset wheeze at 30-42 months of age (OR 1.30 95% CI 1.04-1.61; P = .019), after adjusting for potential

confounders. The association was however no longer significant after adjusting for multiple comparisons. No significant associations were observed for late pregnancy maternal plasma phospholipid fatty acid exposures (n=2945).¹⁵⁵

In a 2011 study of 1275 children from the KOALA Birth Cohort Study who were followed for 6-7 years, no associations were found between maternal plasma phospholipid n-3 fatty acids measured at 34–36 weeks of pregnancy and risk of developing asthma or parentally reported wheeze.¹⁵⁸

In a 2012 study of 1485 healthy mother-infant pairs from the Southampton Women's Survey in the UK who were followed for 6 years, the plasma phospholipid n-3 to n-6 fatty acid ratio was not associated with childhood wheeze, airway inflammation, or childhood FEV₁ (lung function). However, higher maternal EPA, DHA, and total n-3 fatty acids were associated with reduced risk of non-atopic persistent/late wheeze (RR 0.57, 0.67 and 0.69, respectively; P = 0.01, 0.015, and 0.021, resp.). Also, maternal arachidonic acid biomarker was positively associated with airway inflammation (P = 0.024).¹⁶⁸

A 2014 study of 436 infants from the Munich LISApplus birth cohort study in Germany found no significant association between n-3 LC-PUFA or n-6/n-3 ratio in cord blood and risk of asthma at 6 and 10 year follow-up.¹⁵⁶

Observational study subgroup analyses

None of the studies reported subgroup analyses.

Table 24. RCTs for respiratory illness

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Marks et al., 2006¹⁵²</p> <p>Study name: CAPS</p> <p>Study dates: 1997-2004</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 5 years</p> <p>Follow-up article(s)^{164, 165, 151, 166, 153}</p>	<p>Study Population: Pregnant women with allergies</p> <p>Pregnant enrolled 616 Pregnant withdrawals 100 Pregnant completers 516</p> <p>Infants completers 516</p> <p>Race of Mother: NR</p>	<p>Inclusion Criteria: pregnant women whose unborn children were at increased risk of developing asthma because 1 or more parents or siblings had asthma or wheezing</p> <p>Exclusion Criteria: with a pet cat at home, strict vegetarians, women with a nonsingleton pregnancy, and infants born earlier than 36 weeks of gestation. Infants had birth weights less than 2.5 kg, significant congenital malformations, or other significant neonatal disease.</p>	<p>Start time: Infants from the time the child started bottle-feeding, or to solid foods from age 6 months</p> <p>Duration: NR</p> <p>Arm 1: Diet control Description polyunsaturated oils and spreads, containing 40% w6 FA, and sunola oil capsules Manufacturer Crisco-Meadow Lea Foods Inc, Sydney, Australia Blinding The approach to blinding participants and research staff is described in this article's Online Repository at www.jacionline.org.</p> <p>Arm 2: Active Description canola-based oils and spreads, which are low in n-6 fatty acids, and tuna oil capsules, which contain n-3 fatty acids.</p>	<p>Outcome cough without cold</p> <p>Follow-up time 5 years</p> <p>Arm 1 36/249 (14.46%) Arm 2 55/267 (20.6%)</p> <p>Outcome frequent wheeze</p> <p>Follow-up time 5 years</p> <p>Arm 1 4/249 (1.61%) Arm 2 5/267 (1.87%)</p> <p>Outcome probable current asthma</p> <p>Follow-up time 5 years</p> <p>Arm 1 51/249 (20.48%) Arm 2 62/267 (23.22%)</p>
<p>Mihirshahi et al., 2003¹⁵¹</p> <p>Study name: CAPS</p> <p>Study dates: 1997-2002</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Government, Manufacturer supplied product</p> <p>Follow-up: 18 months 1400</p>	<p>Study Population: Pregnant women with allergies</p> <p>Pregnant enrolled 616 (all 4 arms) Pregnant withdrawals 62 Pregnant completers 554</p> <p>Pregnant age: 28.5 (5.3)</p> <p>Race of Mother: NR (96.9%) Other race/ethnicity (Aboriginal 3.1%)</p>	<p>Inclusion Criteria: At least one parent or sibling with symptoms of asthma as assessed by screening questionnaire, Reasonable fluency in English, Telephone at home, Reside within 30 km from center of recruitment</p> <p>Exclusion Criteria: Pet cat at home, Families on strict vegetarian diet, Multiple births, Babies born earlier than 36 weeks gestation, with congenital malformations</p>	<p>Start time: Infants initiation of bottle feeding or 6 months of age</p> <p>Duration: Infants NR</p> <p>Arm 1: Diet Control/HDM control or intervention Brand name Sunola oil Manufacturer Clover Corporation</p> <p>Arm 2: Dietary intervention/HDM control or intervention Description 500mg n-3 rich tuna fish oil supplement Manufacturer Clover Corporation N-3 Composition see Mihirshahi, 2004 table 4 (equivalent to breast milk)</p>	<p>Outcome asthma</p> <p>Follow-up time 18 months</p> <p>Arm 1 31/275 (11.11%) Arm 2 31/279 (11.11%)</p> <p>Outcome wheeze ever</p> <p>Follow-up time 18 months</p> <p>Arm 1 31/275 (11.11%) Arm 2 31/279 (11.11%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Follow-up article(s) ^{164, 165, 166, 152, 153}		or other serious disease, or requiring major surgery or hospitalization for greater than 1 week		
Peat et al., 2004 ¹⁵³ Study name: CAPS Study dates: 2000-2003 Study design: Trial randomized factorial design Location: Australia Funding source / conflict: Industry, Government Follow-up: 3 years 3574, 9131 Follow-up article(s) ^{164, 165, 151, 166, 152}	Study Population: NR Pregnant enrolled 616 Pregnant withdrawals 90 Pregnant completers 526 Pregnant age: Placebo: 29.1 Diet: 28.6 (Placebo: 5.0 Diet: 5.3) NR Race of Mother: NR (100)	Inclusion Criteria: at least 1 parent or sibling with current asthma or frequent wheeze as assessed by screening questionnaire, fluency in English, a telephone at home, and residence within 30 km of the recruitment center. Exclusion Criteria: a pet cat at home, a vegetarian diet, multiple births, and less than 36 weeks gestation.	Start time: Infants 6 months of age Duration: Infants NR Arm 1: Placebo group Description The control group received placebo supplement capsules of Sunola oil containing 83% monounsaturated oils (Clover Corp) and were provided with widely used soybean-based polyunsaturated oils and margarines high in omega-6 fatty acids for use in all food preparation Manufacturer Clover Corp; Goodman Fielder Blinding The research team responsible for recruitment was blind to the methods of randomization until recruitment was complete. the research nurses and research assistants who undertook the outcome assessments, laboratory analyses, and statistical analyses were blind to the group allocation of the participants. Arm 2: Active intervention group Description tuna fish oil capsules Manufacturer Clover Corp; Goodman Fielder Dose 500 mg tuna fish oil capsules daily Total N-3 184 mg	Outcome any asthma Follow-up time 3 years Arm 1 108/259 (41.7%) Arm 2 107/267 (40.07%) Outcome any cough Follow-up time 3 years Arm 1 157/259 (60.62%) Arm 2 132/267 (49.44%) Outcome any wheeze Follow-up time 3 years Arm 1 108/259 (41.7%) Arm 2 107/267 (40.07%)
Atwell et al., 2013 ¹¹⁴ Study name: DINO Study dates: 2001-2005 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied	Study Population: Preterm infants Infants enrolled 657 Infants completers 648 Infant age: birth Race of Mother: White European (90.5%) Other race/ethnicity (9.5%)	Inclusion Criteria: Infants were eligible if born before 33 weeks' gestation Exclusion Criteria: Infants in other trials of fatty acid supplementation, or with major congenital or chromosomal abnormalities, or maternal contraindication for tuna oil ingestion	Start time: Infants birth Duration: Infants to 40 weeks' postmenstrual age (term) Arm 1: Standard DHA Description Placebo/control group (soy oil) N-3 Composition. Dose 6 soy oil capsules/ daily Blinding capsules given to breastfeeding mothers or added to formula DHA 0.35% in preterm formula Arm 2: High DHA Description DHA maternal supplements or	Outcome one or more hospitalizations for lower respiratory conditions Follow-up time 18 months Arm 1 82/335 (24.48%) Arm 2 72/322 (22.36%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
product, Some authors serve on scientific advisory boards for corporations Follow-up: 18 months corrected age Makrides ¹¹³ Follow-up article(s) ^{111, 112, 100, 51, 113, 101, , , , , , ,}		(allergy or coagulopathy) were excluded.	supplemented preterm formula Dose 6 tuna oil capsules daily DHA 900 mg in capsules or 1% infant formula	
Manley et al., 2011 ¹¹² Study name: DINO Study dates: 2001-2007 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations Follow-up: 18 months see above Follow-up article(s) ^{111, 100, 113, 101, 114, , , , , , ,}	Study Population: Preterm infants Breast-feeding women Infants enrolled 657 Infants completers 614 Lactating age: Intervention: 29.9 (5.8) Placebo: 30.2 (5.4) Infant age: 4 days (median) Race of Mother: NR (100%)	Inclusion Criteria: Infants born before 33 weeks' gestation, within 5 days of the infant commencing any enteral feedings. Exclusion Criteria: major congenital or chromosomal abnormalities, from a multiple birth in which not all live-born infants were eligible, enrolled in other trials of fatty acid supplementation, or mother with contraindication to fish oil	Start time: Infants Within 5 days (or less) of starting enteral feeding Duration: Infants NR Arm 1: Standard DHA diet Description Soy bean oil Manufacturer Clover Corporation Dose 6 capsules per day Maternal conditions Infant conditions Current smoker 25% during pregnancy Other maternal conditions 1arm_1_maternal_conditions_other1 Other maternal conditions 2 Birth by C-section: 69% Pre-term birth 100% Low birth weight 18.6% Arm 2: High DHA Description Tuna fish oil Manufacturer Clover Corporation Dose 6 500-mg DHA-rich tuna oil capsules per day Maternal conditions Infant conditions DHA DHA to achieve a breast milk concentration that was 1% of total fatty acids Current smoker 25% during pregnancy Other maternal conditions 1arm_2_maternal_conditions_other1 Other maternal conditions 2 Birth by c-section: 68.3% Other comment 1 If supplementary formula was required, infants were given a high- DHA preterm	Outcome asthma Follow-up time 12 months Arm 1 25/249 (10.04%) Arm 2 18/232 (7.76%) Follow-up time 12 or 18 months Arm 1 53/252 (21.03%) Arm 2 47/237 (19.83%) Follow-up time 18 months Arm 1 46/311 (14.79%) Arm 2 41/292 (14.04%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			formula (approximately 1.0%DHAand 0.6% AA).	
<p>Palmer et al., 2012⁴⁸</p> <p>Study name: DOMInO</p> <p>Study dates: 2006-2009</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Industry, Government, Manufacturer supplied product</p> <p>Follow-up: 9415</p> <p>Follow-up article(s) ^{34, 49, 50, 51, 52, 53, 3}</p>	<p>Study Population: Pregnant women with allergies</p> <p>Pregnant enrolled 706 Pregnant withdrawals 25 Pregnant completers 681</p> <p>Infants enrolled 706 Infants withdrawals 25 Infants completers 681</p> <p>Pregnant age: 29.6 Treatment: 29.6 Placebo: 29.5 (Treatment: 5.7 Placebo: 5.6) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Included if the unborn baby had a mother, father, or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) and they were enrolled from the Women's and Children's Hospital or Flinders Medical Centre in Adelaide.</p> <p>Exclusion Criteria: NR</p>	<p>Start time: Pregnant 21 weeks of gestation Infants 21 weeks of gestation</p> <p>Duration: Pregnant until delivery Infants till delivery</p> <p>Arm 1: Placebo Description 338 women assigned to control supplements-vegetable oil capsules Dose three 500 mg vegetable oil capsules daily Blinding All capsules were similar in size, shape, and colour. . Neither the women nor the research staff were aware of the treatment allocated. Arm 2: n-3 LCPUFA group Description 368 women assigned to fish oil concentrate Brand name Incromega 500 TG Manufacturer Croda Chemicals, East Yorkshire, UK Dose e three 500 mg capsules daily DHA 800mg EPA 100mg</p>	<p>Outcome respiratory tract infection</p> <p>Follow-up time 1 year</p> <p>Arm 1 66/338 (19.53%) Arm 2 65/368 (17.66%)</p>
<p>Palmer et al., 2013⁵³</p> <p>Study name: DOMInO</p> <p>Study dates: 2006-2009 (allergy follow-up to Domino study)</p> <p>Study design: Trial randomized parallel</p> <p>Location: Australia</p> <p>Funding source / conflict: Industry, Government, Some authors serve on scientific advisory boards for corporations</p> <p>Follow-up: 3 years 3170, 3069</p>	<p>Study Population: NR</p> <p>Pregnant enrolled 706 Pregnant completers 638</p> <p>Infants enrolled 706 Infants completers 638</p> <p>Pregnant age: DHA: 28.9 Control: 28.9 (DHA: 5.7) Control: 5.6)</p> <p>Infant age: Birth</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Women whose infants had a parent or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema)</p> <p>Exclusion Criteria: Already taking a prenatal supplement with DHA Fetus had a known major abnormality, Bleeding disorder in which tuna oil was contraindicated, Taking anticoagulant therapy A documented history of drug or alcohol abuse, Participating in another fatty acid trial, Unable to give written</p>	<p>Start time: Pregnant <21 weeks gestation</p> <p>Duration: Pregnant to term</p> <p>Arm 1: Control Description vegetable oil Dose 3 500-mg vegetable oil capsules per day Blinding This was a double-blinded study; all capsules were similar in size, shape and colour Arm 2: Fish oil Brand name Incromega 500 TG, Manufacturer Croda Chemicals, East Yorkshire, England Dose 3 500-mg capsules per day DHA 800 mg per day EPA 100 mg per day</p>	<p>Outcome asthma</p> <p>Follow-up time 3 years</p> <p>Arm 1 5/338 (1.48%) Arm 2 6/368 (1.63%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Follow-up article(s) ^{34, 48, 49, 50, 51, 52, 3} , , , , ,		informed consent, or English was not the main language spoken at home		
Dunstan et al., 2003 ⁵⁷ Study name: Dunstan Study dates: 1999-2001 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government Follow-up: 1 year 4381,6647 Follow-up article(s) ^{42, 56, 58, 59} , , , , ,	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 98 Pregnant withdrawals 15 Pregnant completers 83 Pregnant age: NR (NR) NR Race of Mother: NR (100)	Inclusion Criteria: All women had a history of physician-diagnosed allergic rhinitis and/or asthma and 1 or more positive skin prick tests to common allergens (house dust mite; grass pollens; molds; and cat, dog, and cockroach extracts) Exclusion Criteria: Women were ineligible for the study if they smoked; if they had other medical problems, complicated pregnancies, or seafood allergy; or if their normal dietary intake exceeded 2 meals of fish per week.	Start time: Pregnant 20 weeks of gestation Duration: Pregnant till delivery Arm 1: Placebo group Description 46 women allocated and received placebo-olive oil Manufacturer Pan Laboratories, Moorebank, NSW, Australia Active ingredients 66.6% n-9 oleic acid N-3 Composition. Dose 4 (1-g) capsules of olive oil per day Blinding Randomization and allocation of capsules occurred at a different center separate from the recruitment of participants. Capsules were administered to the participants by someone separate from those doing the allocation. The capsules in the 2 groups were image-matched. Total N-3 <1% n-3 PUFAs Arm 2: Fish oil group Description 52 women were randomized to receive fish oil Manufacturer Ocean Nutrition, Halifax, Nova Scotia, Canada Dose 4 (1g) fish oil capsules per day _x001E_x0007_x0005_x0015_x0013_x0007_x001E_x0013_x000F_ DHA 56.0% EPA 27.7% Total N-3 3.7 g	Outcome asthma Follow-up time 1 year Arm 1 6/43 (13.95%) Arm 2 2/40 (5%) Outcome chronic cough Follow-up time 1 year Arm 1 11/43 (25.58%) Arm 2 5/40 (12.5%) Outcome recurrent wheeze Follow-up time 1 year Arm 1 12/43 (27.91%) Arm 2 10/40 (25%)
D'Vaz et al., 2012 ¹²⁵ Study name: IFOS Study dates: 2005-2009 Study design: Trial randomized parallel	Study Population: Pregnant women with allergies Infants enrolled 420 Infants completers 323 Pregnant age: Placebo:	Inclusion Criteria: Maternal: Pregnant History of doctor diagnosed asthma or allergic rhinitis Skin prick positive to at least one allergen	Start time: Infants Birth Duration: Infants 6 months Arm 1: Placebo Description Olive oil Manufacturer Ocean Nutrition, Ltd Dose 650 mg olive oil	Outcome asthma Follow-up time 12 months Arm 1 0/167 (0%) Arm 2 0/156 (0%) Outcome persistent cough Follow-up time 12 months Arm 1 38/167 (22.75%) Arm 2 42/156 (26.92%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Location: Australia</p> <p>Funding source / conflict: Government, None, Manufacturer supplied product</p> <p>Follow-up article(s) ¹²⁴, Protocol ID 5460</p>	<p>33.2 Fish Oil: 32.5 (Placebo: 4.2 Fish Oil: 4.8)</p> <p>Infant age: Term (39.3 weeks gestation)</p> <p>Race of Mother: NR (100)</p>	<p>Exclusion Criteria: Maternal: Smoking Auto-immune disease Pre-existing medical conditions other than asthma High-risk pregnancy Seafood allergy Fish eaten more than three times per week Fish oil supplementation already taken (in excess of 1000 mg per day) Exclusion from data analysis criteria due to protocol deviations: Pre-term delivery (gestation <36 weeks) Infant with congenital abnormalities or significant disease not related to intervention</p>	<p>Blinding Randomization was completed by external staff via computer software using an unpredictable allocation sequence, stratified according to maternal and paternal atopic history and parity. Mothers and study personnel were unaware of the group allocation.</p> <p>Maternal conditions Maternal allergies 100 Arm 2: Fish oil group Manufacturer Ocean Nutrition Ltd. Purity Data fatty acid composition remained unchanged over the study period Dose 1 capsule contents, to be administered orally, prior to feeding in the morning Maternal conditions DHA 280 mg EPA 110 mg Maternal allergies 100</p>	<p>Follow-up time 6 months Arm 1 27/167 (16.17%) Arm 2 19/156 (12.18%) Outcome recurrent wheeze Follow-up time 12 months Arm 1 16/167 (9.58%) Arm 2 21/156 (13.46%) Follow-up time 6 months Arm 1 27/167 (16.17%) Arm 2 23/156 (14.74%)</p>
<p>Furuhjelm et al., 2011¹⁴⁸</p> <p>Study name: NR</p> <p>Study dates: 2003-2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: Sweden</p> <p>Funding source / conflict: Industry</p> <p>Follow-up: 2 years 4378</p> <p>Follow-up article(s) ¹⁴⁹, ¹⁶⁷</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117</p> <p>Infants enrolled 145 Infants withdrawals 28 Infants completers 117</p> <p>Pregnant age: NR (NR) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: family history of current or previous allergic symptoms, i.e. bronchial asthma, eczema, allergic food reactions, itching and running eyes and nose at exposure to pollen, pets or other known allergens.</p> <p>Exclusion Criteria: Allergy to soya or fish, treatment with anticoagulants or omega-3 fatty acid supplements.</p>	<p>Start time: Pregnant 25 weeks of gestation</p> <p>Duration: Pregnant 15 weeks (i.e., until delivery)</p> <p>Arm 1: Placebo Description soya bean oil Manufacturer Pharma Nord, Vejle, Denmark Active ingredients 58% linoleic acid (LA), 2.5 g/day Viability the antioxidant a-tocopherol (placebo: 36 mg/day) to assure the stability of the oil N-3 Composition. Dose nine capsules a day Blinding The mothers, as well as the staff handling clinical and laboratory follow-up, were blinded to group allocation, and the mothers were identified by their study number only. ALA 6%, 0.28 g/day Arm 2: w-3 group Description w-3 fatty acids Viability the antioxidant a-tocopherol (w-3 group: 28 mg/day) to assure the stability of the oil N-3 Composition DHA & EPA</p>	<p>Outcome any asthma Follow-up time 2 years Arm 1 8/65 (12.31%) Arm 2 7/54 (12.96%) Outcome any rhinoconjunctivitis Follow-up time 2 years Arm 1 2/65 (3.08%) Arm 2 2/54 (3.7%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Dose nine capsules a day DHA 25% DHA, 1.1 g/day EPA 35% EPA, 1.6 g/day	
<p>Imhoff-Kunsch et al., 2011¹⁷¹</p> <p>Study name: NR</p> <p>Study dates: February 2005 - February 2007</p> <p>Study design: Trial randomized parallel</p> <p>Location: Mexico</p> <p>Funding source / conflict: Government, March of Dimes</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 1094 Pregnant completers 851</p> <p>Infants enrolled 851 Infants completers 834</p> <p>Pregnant age: DHA: 26.3 Placebo: 20.5 (DHA: 4.9 Placebo: 1.9)</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: Women were considered for inclusion in the study if they were in gestation week 18 to 22, were aged 18 to 35 years, planned to deliver at the IMSS General Hospital in Cuernavaca, planned to predominantly breastfeed for at least 3 months, and planned to live in the area for 2 years after delivery</p> <p>Exclusion Criteria: Exclusion criteria included (1) high-risk pregnancy, (2) lipid metabolism/absorption disorders, (3) regular intake of fish oil or DHA supplements, or (4) chronic use of certain medications.</p>	<p>Start time: Pregnant 18 to 22 weeks gestation</p> <p>Duration: Pregnant until parturition</p> <p>Arm 1: Placebo Description Placebo/control corn and soy oil capsule Dose 2 capsules daily Blinding The placebo capsules, which were similar in appearance and taste to the DHA capsules, contained a corn and soy oil blend with no added antioxidants....All participants and members of the study team were blinded to the treatment scheme throughout the intervention period of the study. Data were unblinded for the analytical study team after the last infant in the study was born and had reached the age of 6 months.</p> <p>Arm 2: DHA Description DHA capsule Manufacturer Martek Biosciences Corporation, Columbia, MD Dose 2 capsules daily DHA 200mg/ capsule</p>	<p>Outcome cold (any of cough, phlegm, nasal congestion, nasal secretion) Follow-up time 1 month (preceding 15 days) Arm 1 190/427 (44.6%) Arm 2 159/422 (37.6%) Follow-up time 3 months Arm 1 185/419 (44.1%) Arm 2 157/415 (37.8%) Follow-up time 6 months (preceding 15 days) Arm 1 193/414 (46.6%) Arm 2 194/420 (46.2%) Outcome cough Follow-up time 1 month (preceding 15 days) Arm 1 47/427 (11%) Arm 2 40/422 (9.5%) Follow-up time 3 months Arm 1 100/419 (23.9%) Arm 2 80/415 (19.3%) Follow-up time 6 months (preceding 15 days) Arm 1 136/414 (32.9%) Arm 2 139/420 (33.1%) Outcome difficulty breathing Follow-up time 1 month (preceding 15 days) Arm 1 10/427 (2.3%) Arm 2 10/422 (2.4%) Follow-up time 3 months Arm 1 10/419 (2.4%) Arm 2 12/415 (2.9%) Follow-up time 6 months (preceding 15 days) Arm 1 7/414 (1.7%) Arm 2 6/420 (1.4%) Outcome nasal congestion Follow-up time 1 month (preceding 15 days)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				<p>Arm 1 140/427 (32.8%) Arm 2 119/422 (28.2%) Follow-up time 3 months Arm 1 119/419 (28.4%) Arm 2 104/415 (25.1%) Follow-up time 6 months (preceding 15 days) Arm 1 116/414 (28%) Arm 2 124/420 (29.6%) Outcome nasal secretion Follow-up time 1 month (preceding 15 days) Arm 1 46/427 (10.8%) Arm 2 30/422 (7.1%) Follow-up time 3 months Arm 1 72/419 (17.2%) Arm 2 62/415 (14.9%) Follow-up time 6 months (preceding 15 days) Arm 1 122/414 (29.5%) Arm 2 118/420 (28.2%) Outcome phlegm Follow-up time 1 month (preceding 15 days) Arm 1 82/427 (19.2%) Arm 2 71/422 (16.8%) Follow-up time 3 months Arm 1 78/419 (18.6%) Arm 2 81/415 (19.5%) Follow-up time 6 months (preceding 15 days) Arm 1 100/414 (24.2%) Arm 2 100/420 (23.9%) Outcome wheezing Follow-up time 1 month (preceding 15 days) Arm 1 30/427 (7%) Arm 2 35/422 (8.3%) Follow-up time 3 months Arm 1 34/419 (8.1%) Arm 2 29/415 (7%) Follow-up time 6 months (preceding 15 days)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1 45/414 (10.9%) Arm 2 50/420 (11.9%)
<p>Olsen et al., 2008¹⁷⁰</p> <p>Study name: NR</p> <p>Study dates: 1989-2006</p> <p>Study design: Trial randomized parallel</p> <p>Location: Denmark</p> <p>Funding source / conflict: NR</p> <p>Follow-up: 16 years reference 209 in original report</p> <p>Follow-up article(s) linked to ref 209 in original report per Sydne</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 533</p> <p>Infants enrolled 531</p> <p>Infants completers 522</p> <p>Pregnant age: Fish oil: 29.4 Olive oil: 29.7 No oil: 29.1 (Fish oil: (4.4) Olive oil: (4.3) No oil: (4.1)) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Women seen in the main midwife clinic in Aarhus Denmark at week 30 gestation</p> <p>Exclusion Criteria: History of placental abruption in a previous pregnancy or a serious bleeding episode in the current pregnancy; multiple pregnancies; allergy to fish; regular use of fish oil pr prostaglandin inhibitors</p>	<p>Start time: Pregnant 30 weeks gestation</p> <p>Duration: Pregnant to term</p> <p>Arm 1: Control Description Olive oil Active ingredients 72% oleic acid N-3 Composition. Dose 4 one gram capsules Blinding Gelatin capsules were coloured, and the capsules and their boxes looked identical. ALA 12% Arm 2: Fish oil Brand name Pikasol Fish Oil Manufacturer Lube Limited Active ingredients 2mg tocopherol/ml N-3 Composition 2.7g marine n-3PUFA/day Dose 4 1-gm capsules EPA 32% EPA-DHA 23% Arm 3: No oil Description no intervention at all</p>	<p>Outcome asthma (all types) Follow-up time 16 years Arm 1 11/136 (8.09%) Arm 2 8/263 (3.04%) Arm 3 3/129 (2.33%) Outcome asthma (allergic) Follow-up time 16 years Arm 1 8/136 (5.88%) Arm 2 2/263 (0.76%) Arm 3 0/129 (0%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
<p>Escamilla-Nunez et al., 2014⁷²</p> <p>Study name: POSGRAD</p> <p>Study dates: 2005-2009</p> <p>Study design: Trial randomized parallel</p> <p>Location: Mexico</p> <p>Funding source / conflict: Government</p> <p>Follow-up: 18 months ³¹</p> <p>Follow-up article(s) ^{32, 31}</p>	<p>Study Population: Pregnant women with allergies</p> <p>Pregnant enrolled 1,040 Pregnant completers 973</p> <p>Pregnant age: 26.3 (4.8) 18-35</p> <p>Race of Mother: Hispanic (100% Mexican)</p>	<p>Inclusion Criteria: Maternal age 18 - 35 years, recruited between 18 and 22 weeks of gestation. Willingness to breastfeed exclusively or predominantly during at least the first 3 months of life of the newborn and with the intention to live in their area of residence for at least 2 years after delivery</p> <p>Exclusion Criteria: High-risk pregnancies (pregnancy complications, including premature placental abruption, preeclampsia, pregnancy-induced hypertension, severe bleeding episode in pregnancy or lipid absorption disorders; Regular consumption of fish oil or DHA supplements; Chronic use of certain medications (eg, drugs for epilepsy)</p>	<p>Start time: Pregnant 18-22 weeks gestation</p> <p>Duration: Pregnant to term</p> <p>Arm 1: Placebo Description olive oil capsule Dose 2 capsules per day</p> <p>Arm 2: DHA Description Algal DHA Manufacturer Martek Biosciences Dose 2 capsules of 200mg each DHA 200 mg algal DHA/capsule</p>	<p>Outcome breathing difficulty Follow-up time 18 months Arm 1 48/440 (10.91%) Arm 2 47/429 (10.96%)</p> <p>Outcome cough Follow-up time 18 months Arm 1 1151/440 (261.59%) Arm 2 1178/429 (274.59%)</p> <p>Outcome phlegm with congestion and/or nasal discharge, fever with phlegm and congestion and/or nasal discharge, or wheezing with fever Follow-up time 18 months Arm 1 49/440 (11.11%) Arm 2 48/429 (11.11%)</p> <p>Outcome wheezing Follow-up time 18 months Arm 1 262/440 (59.55%) Arm 2 252/429 (58.74%)</p>
<p>Noakes et al., 2012¹⁵⁰</p> <p>Study name: SiPS</p> <p>Study dates: NR</p> <p>Study design: Trial randomized parallel</p> <p>Location: UK</p>	<p>Study Population: Healthy pregnant women</p> <p>Pregnant enrolled 123 Pregnant withdrawals 37 Pregnant completers 86</p> <p>Pregnant age: Mean(SEM)(n):Control group -28.4 (0.6)(61); Salmon group- 29.5(0.5)</p>	<p>Inclusion Criteria: age 18–40 y; >19 wk gestation; healthy uncomplicated singleton pregnancy; infant at risk of atopy (one or more first-degree relatives of the infant affected by atopy, asthma or allergy by self-report); consumption of < 2</p>	<p>Start time: Pregnant 20 weeks of gestation</p> <p>Duration: Pregnant until birth</p> <p>Arm 1: Control group Description Women in the control group (n = 61) were asked to continue their habitual diet Blinding Researchers responsible for assessing outcome measures (both laboratory and clinical) remained blinded to the groups</p> <p>Arm 2: Salmon group</p>	<p>Outcome chest infection Follow-up time 6 months Arm 1 1/46 (2.17%) Arm 2 3/37 (8.11%)</p> <p>Outcome pneumonia/bronchiolitis Follow-up time 6 months Arm 1 1/46 (2.17%) Arm 2 1/37 (2.7%)</p> <p>Outcome wheeze Follow-up time 6 months Arm 1 11/46 (23.91%)</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Government, None	(62) (NR) 18-40 years Race of Mother: NR (100)	portions oily fish per month, excluding tinned tuna; and no use of fish-oil supplements currently or in the previous 3 months. Exclusion Criteria: age <18 or >40 y; <19 wk gestation; no first-degree relatives of the infant affected by atopy, asthma, or allergy; consumption of >2 portions oily fish per month, excluding tinned tuna; use of fish-oil supplements within the previous 3 mo; participation in another research study; known diabetes; presence of any autoimmune disease; learning disability; terminal illness; and mental health problems.	Description Women in the salmon group (n = 62) were asked to incorporate 2 portions of farmed salmon (150 g/portion) into their diet per week Active ingredients 30.5 g protein, 16.4 g fat, 4.1 mg alpha-tocopherol, 1.6 mg gamma-tocopherol, 6 micro-g vitamin A, 14 micro-g vitamin D3, and 43 micro-g Selenium Dose two 150-g portions per week DHA 1.16 g per portion EPA 0.57g per portion EPA-DHA 1.73 per portion Total N-3 3.56g per portion Other comment 1 Docosapentaenoic acid-0.35g	Arm 2 7/37 (18.92%)

Table 25. Observational studies for respiratory illness

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Wijga, et al., 2006¹⁵⁴</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 276 Pregnant withdrawals 11 Pregnant completers 265</p> <p>Infants enrolled 276 Infants withdrawals 11 Infants completers 265</p> <p>Pregnant age: 31.0 (3.9) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Mothers reporting at least 1 of the following: (a history of) asthma, current hay fever, current allergy for pets, or current allergy for house dust or house dust mite were defined as allergic, and mothers reporting that they had none of these were defined as nonallergic.</p> <p>Exclusion Criteria: NR</p>
<p>Newson, et al., 2004¹⁵⁵</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: UK</p> <p>Funding source / conflict: Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 4136</p> <p>Infants enrolled 4202</p> <p>Infant age: NR (NR) NR</p> <p>Race of Mother: NR (100%)</p>	<p>Inclusion Criteria: Women were enrolled as early in pregnancy as possible on the basis of an expected date of delivery between April 1, 1991, and December 31, 1992, and place of residence within the 3 Bristol-based health districts of the former county of Avon, United Kingdom</p> <p>Exclusion Criteria: NR for enrollment. Exclusion for analysis: We excluded 722 children from the maternal fatty acid analyses and 216 children from the cord fatty acid analyses who were from multiple pregnancies or who were in small missing value categories for various confounders.</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Standl, et al., 2014¹⁵⁶</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Germany</p> <p>Funding source / conflict: Government</p> <p>Follow-up article(s) supplemental materials</p>	<p>Study Population: Healthy infants</p> <p>Infants enrolled 436 Infants completers 243</p> <p>Mother age: 32.7 (3.9) NR</p> <p>Infant age: NR (NR) NR</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: Neonates displaying at least one of the following criteria: preterm birth (maturity <37 gestational weeks), low birth weight (<2,500 g), congenital malformation, symptomatic neonatal infection, antibiotic medication, hospitalization or intensive medical care during neonatal period. In addition, newborns from mothers with immune-related diseases (autoimmune disorders, diabetes, hepatitis B), on long-term medication or who abuse drugs and/or alcohol, and newborns from parents with a nationality other than German or who were not born in Germany, were excluded.</p>
<p>Lumia, et al., 2011¹⁶⁹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: NR</p> <p>Location: Finland</p> <p>Funding source / conflict: Industry, Government, Multiple foundations and Societies, None</p> <p>Follow-up: Baseline article not included</p>	<p>Study Population: NR</p> <p>Infants enrolled 2680 Infants completers 2679</p> <p>Pregnant age: 14.8% <25 years at birth 35.4% 25-29 years 30.4% 30-34 years 19.5% ≥35 years</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: infants at three university hospitals in Finland (Turku, Tampere and Oulu) whose cord blood was screened for HLA-conferred genetic susceptibility to type 1 diabetes (HLA-DQB1) and were found to have high or moderate genetic risk of type 1 diabetes</p> <p>Exclusion Criteria: Severe congenital malformations or diseases, parents of non-Caucasian origin or parents who did not have a working knowledge of Finnish, Swedish or English</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Morales, et al., 2012¹⁶³</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Spain</p> <p>Funding source / conflict: Government</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Pregnant enrolled 622 Pregnant completers 580</p> <p>Infants enrolled 622 Infants completers 580</p> <p>Mother age: 31.6 (4.2)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: to be resident in the study area, to be at least 16 years old, to have a singleton pregnancy, to not have followed any programme of assisted reproduction, to wish to deliver in the reference hospital, and to have no communication problems</p> <p>Exclusion Criteria: NR</p>
<p>Miyake, et al., 2009¹⁶¹</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Japan</p> <p>Funding source / conflict: Government, None</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 1,002 Pregnant completers 763</p> <p>Infants enrolled 1,002 Infants completers 763</p> <p>Pregnant age: 30.0 (4.0)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: pregnant women living in Neyagawa City, Osaka Prefecture or the surrounding cities</p> <p>Exclusion Criteria: Not reported</p>
<p>Miyake, et al., 2013¹⁶²</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Japan</p> <p>Funding source / conflict: Industry, Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 1757 Pregnant completers 1354</p> <p>Infants enrolled 1757 Infants completers 1354</p> <p>Pregnant age: 31.5 (4.1)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: Women living in one of 7 prefectures on Kyushu Island who became pregnant from 2007-2008</p> <p>Exclusion Criteria: Failure to complete the study surveys</p>

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria
<p>Notenboom, et al., 2011¹⁵⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: Netherlands</p> <p>Funding source / conflict: Industry, Government, Multiple foundations and Societies</p>	<p>Study Population: Healthy infants Healthy pregnant women</p> <p>Infants enrolled 1275 Infants completers 1253</p> <p>Mother age: 32.6 (3.8)</p> <p>Race of Mother: White European (Dutch 96.3%)</p>	<p>Inclusion Criteria: A detailed description of the design has been provided elsewhere [12]... The present study population consists of participants recruited from January 2002 onwards who consented to biosampling. Maternal blood samples (n= 1374) were taken in the 34th–36th week of pregnancy and venous blood samples from their offspring at age 24 months (n= 815)</p> <p>Exclusion Criteria: Current multiple pregnancy n=9 Prematurity n=15 Perinatal infant death n=2 Down syndrome n=4 No response after birth n=51</p>
<p>Pike, et al., 2012¹⁶⁸</p> <p>Study name: NR</p> <p>Study dates: NR</p> <p>Study design: Observational prospective</p> <p>Location: UK</p> <p>Funding source / conflict: Government, Some authors serve on scientific advisory boards for corporations</p>	<p>Study Population: Healthy infants</p> <p>Pregnant enrolled 1485</p> <p>Infants enrolled 1485 Infants completers 865</p> <p>Pregnant age: 30.4 (3.8)</p> <p>Race of Mother: NR (100)</p>	<p>Inclusion Criteria: mothers and children in the Southampton Women's Survey</p> <p>Exclusion Criteria: Infants born ≥ 35 weeks' gestation were excluded to avoid abnormal lung development associated with prematurity</p>

Key Question 3: Maternal or childhood adverse events:

- What are the short and long term risks related to maternal intake of n-3s during pregnancy or breastfeeding on
 - Pregnant women
 - Breastfeeding women
 - Term or preterm human infants at or after birth
- What are the short and long term risks associated with intakes of n-3s by human infants (as maternal breast milk or infant formula supplemented with n-3 FA)?
- Are adverse events associated with specific sources or doses?

Key Points

Antenatal supplementation

- Among eight RCTs that reported on maternal adverse events associated with prenatal supplementation, two provided no usable data, three reported no difference between intervention groups, and three reported increased GI complaints in the n-3 FA supplemented groups. Among three RCTs that reported on infant AEs associated with antenatal maternal supplementation, one study found no difference between groups, except for longer duration of two types of symptoms in infants of supplemented mothers; another study found a decrease in risk for SAEs among infants of supplemented mothers; and a third found a small but significant increase risk for respiratory distress among infants of supplemented mothers but no other differences.

Supplementation of preterm infants

- Among four RCTs reporting on AEs in supplemented preterm infants, no differences were observed in SAEs or AEs (except for an increase in gas in one study, compared with placebo). Two reported no differences in adverse outcomes known to be associated with preterm birth, and one reported no differences in such outcomes with the exception of two findings.

Supplementation of healthy term infants

- Among five RCTs reporting on AEs in supplemented healthy term infants, two studies reported a significant increase in non-serious AEs in the placebo group, and only one study, a dose-response assessment of DHA, reported an increase in the incidence of an AE, watery eyes, in infants receiving the middle dose of DHA

Description of Included Studies

A total of 16 RCTs described or reported assessing adverse events in 18 publications.^{30, 31, 34, 43, 94, 103, 104, 107-110, 113, 123, 126, 132, 148, 149, 171} Seven of the 17 administered supplements to pregnant or breastfeeding women,^{30, 31, 34, 43, 94, 148, 149, 171} and 11 administered supplements to infants.^{103, 104, 107-110, 113, 123, 126, 132} One study administered supplements to both mothers and infants).¹⁴⁹ This study reported only one adverse event that was not attributed to supplementation with either the intervention or placebo formula. We identified no observational studies that reported on adverse effects of exposure to n-3 FA.

Maternal Supplementation

Maternal Outcomes

Of the studies that conducted maternal interventions and reported on maternal outcomes, one reported no adverse events by study arm¹⁴⁸ and one did not identify the AEs or attribute them to a study arm⁹⁴. Incidence of maternal AEs in four of the remaining five studies did not differ between intervention and placebo groups.

A 2003 study randomized 89 breastfeeding women at risk for postpartum depression to 0.2g/d DHA or placebo in the immediate postpartum period; the duration of the intervention was 4 months. The study reported that no women withdrew because of adverse effects of the supplement.⁹⁴

A 2010 study in Sweden randomized 145 pregnant women in the 25th week of gestation to fish oil capsules that provided 1.6g EPA and 1.1g DHA per day or soy bean oil capsules as placebo; supplementation continued through 3.5 months postpartum. This study did not report AEs by study arm.^{148, 149}

A 2013 U.S. Phase III RCT randomized 350 pregnant women to supplements containing 40% DHA (percent of total fats by weight) and 5% AA (the placebo contained ALA and DHA). This study found no significant differences between intervention groups in any of 13 categories of maternal AEs and SAEs.³⁰

A 2010 multisite Australian trial, the DOMInO trial, randomized 2,399 women at less than 21 weeks gestation to daily supplements of 0.8g/d DHA or placebo through term.³⁴ The authors reported more gastrointestinal distress but less diarrhea among the women who received DHA-containing supplements. This study also reported no serious adverse events (SAEs) in the mothers.³⁴

A 2010 study in Mexico randomized 1,094 pregnant women at 18 to 22 weeks gestation to a supplement of 0.4 g/d algal DHA or a placebo. This study reported no difference in the incidence of vomiting or nausea between the two groups and reported no SAEs among mothers.³¹

A 2010 U.S. study randomized 852 women at high risk of recurrent preterm birth to a daily supplement (1.2g/d EPA: 0.8g/d DHA) or matching placebo from 16 to 22 through 36 weeks of gestation, and reported an increase in gastrointestinal complaints among n-3 supplemented mothers (burping, p=0.001, vomiting p=0.005, bad taste p=0.002).⁴³

Infant Outcomes

Among studies with maternal supplementation that reported on infant outcomes, four reported on AEs in infants. One of the four found no differences in a large number of infant birth-associated AEs.³⁰

A 2010 study in Mexico randomized 1,094 pregnant women at 18 to 22 weeks gestation to a supplement of 0.4 g/d algal DHA or a placebo. The effects of maternal supplementation on infant health and adverse health outcomes were assessed at birth³¹ and at 1, 3, and 6 months.¹⁷¹ At birth, total AEs and SAEs (including congenital anomalies) did not differ between groups of infants.³¹ Maternal reports of symptoms of illnesses and duration of illnesses, including fever, vomiting, diarrhea, rash and other illnesses did not differ between groups at 1, 3, or 6 months of age. However, the relative risk of longer duration of rash was greater for infants of DHA-supplemented mothers than for infants of control mothers at 1 month (RR1.22[1.05, 1.41]); the relative risk for longer duration of “other illnesses” was less for infants of DHA-supplemented mothers at 3 months (RR 0.77[0.62, 0.95]), and at 6 months, the relative risk for longer duration

of vomiting was greater (RR 1.74[1.19, 2.54]) and for rash (RR 0.77[0.64, 0.94]) and other illnesses (0.75[0.59, 0.94]) was less for infants of DHA-supplemented mothers.¹⁷¹

A 2010 multisite Australian trial, the DOMInO trial, randomized 2,399 women at less than 21 weeks gestation to daily supplements of 0.8g/d DHA or placebo through term.³⁴ The authors reported fewer SAEs among infants of n-3 FA supplemented mothers than among infants of mothers who received the placebo supplements during the first 18 months of life, including a decreased risk for any admission to a neonatal intensive care unit (RR 0.57[0.34, 0.97]) and decreased risk for death (RR 0.33[0.11, 1.03]). No difference in the risk for major congenital anomalies was observed between the groups.³⁴

A 2010 U.S. study randomized 852 women at high risk of recurrent preterm birth to a daily supplement (1.2g/d EPA: 0.8g/d DHA) or matching placebo from 16 to 22 through 36 weeks of gestation. This study observed an increase in the risk for respiratory distress at birth among infants of the n-3 FA supplemented mothers compared with infants of mothers given the placebo supplement, but no other differences between the groups.⁴³

Infant Supplementation

Among studies of infant supplementation alone, four enrolled preterm infants, and five enrolled healthy term infants. All randomized infants to a supplement containing combinations of DHA and AA.

Preterm Infants

A small study conducted in Taiwan that randomized 27 larger preterm infants to receive formula supplemented with 0.05% DHA and 0.1% AA or the identical formula without LCPUFA reported no SAEs in either group over the first year of life.¹²⁶

A multisite Australian study that randomized 657 preterm infants to higher-concentration DHA formula (1.0% DHA and 0.6% AA) or lower-concentration DHA formula (0.6% DHA 0.6% AA) compared adverse birth outcomes associated with prematurity between groups, and observed no difference in rates of mortality, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), intraventricular hemorrhage, seizures, blindness, hearing loss, or need for oxygen.¹¹³

A 2005 U.S. study that randomized preterm infants to one of three infant formulas supplemented with algal DHA (0.017g/100 ml) and AA (0.034 g/100ml), the same concentrations of fish DHA and algal AA, or placebo oils also reported no difference among the groups with respect to parental reports of fussiness, diarrhea, or constipation (data not shown), but more gas than usual among the algal DHA and fish DHA-supplemented groups of infants at 40 weeks and 44 weeks post-menstrual age ($p < 0.05$) but no differences at 53 or 57 weeks.¹⁰⁴ This study also found no differences in multiple adverse outcomes that are associated with preterm birth.

A 2008 study in Norway that randomized preterm infants to a supplement added to breast milk (0.032g DHA and 0.031 g AA or placebo per 100 ml milk) found no difference in “registered” AEs between the groups.¹⁰³ However, the study reported a non-statistically significant increase in two adverse outcomes associated with preterm birth in the infants who received supplemented milk: longer duration of need for both nasal continuous positive airway pressure treatment (28 vs 13 days) and oxygen (13 vs 8 days).

Healthy Term Infants

Included studies of healthy term infants recruited, randomized, and initiated interventions in the first week of life.

A 2005 U.S. study randomized 103 healthy term infants (born at one of two hospitals) to two commercial infant formula products: Enfamil with iron supplemented with DHA (0.36% of total fatty acids) and AA (0.72% of total fatty acids) or not supplemented.¹⁰⁷ Withdrawal from the study due to gastrointestinal intolerance of the study formula or to illness not attributable to the formula was assessed over 12 months; at no time did withdrawal from the supplemented formula group due to gastrointestinal effects significantly exceed that of the group receiving control formula. Likewise, withdrawal due to other infant conditions was the same across study groups.

A 2007 multisite U.S. study randomized 244 healthy term infants to receive a soy formula fortified with 0.017g DHA/100 kcal from algal oil and 0.034g AA/100 kcal or a control formula for 4 months.¹¹⁰ No significant differences were observed between groups for AEs except for the following: gastrointestinal reflux was higher in the controls than in the supplemented group ($p = 0.009$); the incidence of metabolic or nutritional difficulties (weight loss, poor weight gain, and Type 1 glutaric acidemia) was higher in controls than in the supplemented group ($p = 0.013$). The numbers of SAEs were the same for each group, and none were attributed to the study products.

A 2008 Canadian study randomized 30 healthy term infants to one of two formulas: S-26 Gold supplemented with 0.2% DHA and 0.34% AA (by weight) or the same formula without LCPUFA.¹⁰⁸ The authors reported no difference between the groups in the incidence of non-serious AEs (e.g., gas, spit-ups, cramps, vomiting, mucus or blood in stools) as reported by mothers or in laboratory values at 2 or 6 weeks.

The 2010 DIAMOND study, a multisite U.S. study, randomized healthy term infants to receive formula supplemented with one of three levels of DHA (0.32%, 0.64%, and 0.96%) and 0.64% AA. No differences were observed in the proportions of infants with at least one AE; in any of the 86 symptoms assessed, with the exception of watery eyes (increased only in the 0.64% DHA group); and in the numbers with at least one SAE.¹³² The association between one case of sepsis in an infant in the 0.64% DHA group and diet could not be definitively established.

A 2014 study in Serbia randomized 213 healthy term infants to one of two types of formula: a standard formula fortified with DHA and AA (0.011g/100kcal each) or the same formula without LCPUFA (a reference group was breastfed).¹⁰⁹ At 4 months of age, the incidence of total AEs was nearly 50% higher in the infants receiving the control formula (45 percent) than in the infants receiving the fortified formula (24%, $p=0.003$). The proportion of infants who experienced non-serious AEs was three times higher in the control group as in the fortified formula group (41.3 percent vs. 13.6 percent), although the proportions of AE by type were similar across the two groups (e.g., 50 percent were respiratory tract infections, 24 percent were skin infection/eczema, and 10 percent were gastrointestinal problems). The proportion of infants who experienced an SAE was higher in the intervention group than in the control group (10.2 percent vs. 3.3 percent), but the authors attributed only one SAE per group (a combination of gastrointestinal complaints) to formula consumption.

Table 26. Adverse Events

Author, Year, Study	Intervention group and Adverse Event
Imhoff-Kunsch et al., 2011 ¹⁷¹	<p>Intervention:</p> <p>congenietal anomalie at birth DHA 16/547 (2.93%) control 15/547 (2.74%)</p> <p>infant deaths DHA 4/547 (0.73%) control 8/547 (1.46%)</p> <p>nausea DHA 184/547 (33.7%) control 166/547 (30.3%)</p> <p>serious adverse event DHA 25/547 (4.57%) control 21/547 (3.84%)</p> <p>stillbirths DHA 2/547 (0.37%) control 3/547 (0.55%)</p> <p>vomiting DHA 147/547 (26.9%) control 130/547 (23.8%)</p>
Agostoni et al., 2009 ¹²³	<p>Intervention: Healthy term infants</p> <p>any adverse event Intervention 0/580 (0%) control 0/580 (0%)</p>

Author, Year, Study	Intervention group and Adverse Event
Fleddermann et al., 2014 ¹⁰⁹	Intervention: Healthy term infants
Name of study: BeMIM (Belgrade-Munch Infant Milk Tri	<p>formula associated serious AE Breast-fed 0/45 (0%) Control 1/92 (1.09%) Intervention 1/88 (1.14%)</p> <p>gastrointestinal Breast-fed 2/45 (4.44%) Control 6/92 (6.52%) Intervention 1/88 (1.14%)</p> <p>not formula associated serious AE Breast-fed 4/45 (8.89%) Control 2/92 (2.17%) Intervention 8/88 (9.09%)</p> <p>others Breast-fed 5/45 (11.11%) Control 3/92 (3.26%) Intervention 3/88 (3.41%)</p> <p>respiratory Breast-fed 18/45 (40%) Control 21/92 (22.83%) Intervention 6/88 (6.82%)</p> <p>skin Breast-fed 14/45 (31.11%) Control 7/92 (7.61%) Intervention 1/88 (1.14%)</p> <p>total AE Breast-fed 45/45 (100%) Control 41/92 (44.57%) Intervention 21/88 (23.86%)</p> <p>total non serious AE Breast-fed 41/45 (22.2%) Control 38/92 (41.3%) Intervention 12/88 (13.6%)</p> <p>total serious AE Breast-fed 4/45 (2.2%) Control 3/92 (3.3%) Intervention 9/88 (10.2%)</p> <p>urinary tract Breast-fed 2/45 (4.44%) Control 1/92 (1.09%) Intervention 1/88 (1.14%)</p>

Author, Year, Study	Intervention group and Adverse Event
<p>Birch et al., 2010¹³²</p> <p>Name of study: Diamond</p>	<p>Intervention: Infant</p> <p>at least one adverse event 0.32 % DHA 76/83 (91.57%) 0.64 % DHA 80/84 (95.24%) 0.96% DHA 80/87 (91.95%) control 75/85 (88.24%)</p> <p>at least one serious adverse event 0.32 % DHA 6/83 (7.23%) 0.64 % DHA 6/84 (7.14%) 0.96% DHA 6/87 (6.9%) control 7/85 (8.24%)</p> <p>infant watery eyes 0.32 % DHA 1/83 (1.2%) 0.64 % DHA 4/84 (4.76%) 0.96% DHA 0/87 (0%) control 0/85 (0%)</p> <p>report of sepsis 0.32 % DHA 0/83 (0%) 0.64 % DHA 1/84 (1.19%) 0.96% DHA 0/87 (0%) control 0/85 (0%)</p>
<p>Field et al., 2008¹⁰⁸</p>	<p>Intervention: Infant</p> <p>"no difference among groups in the incidence of minor adverse events (gas, spit-ups, cramps, vomiting and mucus or blood in stools) ./ . (%)</p>
<p>Carlson et al., 2013³⁰</p> <p>Furuhjelm et al., 2011¹⁴⁸</p>	<p>Intervention: Maternal</p> <p>discontinuation due to abdominal pain 3/145 (2.07%)</p> <p>discontinuation due to inability to swallow capsule 9/145 (6.21%)</p> <p>discontinuation due to nausea 6/145 (4.14%)</p>

Author, Year, Study	Intervention group and Adverse Event
<p>Makrides et al., 2010³⁴</p> <p>Name of study: DOMInO</p>	<p>Intervention: Maternal</p> <p>infant at least one adverse event (admission to level III (intensive care) hospital treatment, major congenital abnormality, or death) DHA 36/1197 (3.01%) control 54/1202 (4.49%)</p> <p>infant death DHA 4/1197 (0.33%) control 12/1202 (1%)</p> <p>infant major congenital abnormality DHA 15/1197 (1.25%) control 11/1202 (0.92%)</p> <p>infant with any admission to neonatal intensive care DHA 21/1197 (1.75%) control 37/1202 (3.08%)</p> <p>mother any level III antenatal hospitalization DHA 2/1197 (0.17%) control 2/1202 (0.17%)</p> <p>mother death DHA 0/1197 (0%) control 0/1202 (0%)</p>
<p>Llorente et al., 2003⁹⁴</p> <p>Name of study: Unnamed Trial A</p>	<p>Intervention: Maternal</p> <p>no withdrawals due to adverse events DHA 0/44 (0%) placebo 0/45 (0%)</p>
<p>Ramakrishnan et al., 2010³¹</p> <p>Name of study: POSGRAD</p>	<p>Intervention: Maternal</p> <p>infant born with congenital anomalies (spina bifida, heart malformations, considered unrelated to intervention) DHA 16/547 (2.93%) control 15/547 (2.74%)</p> <p>infant death DHA 4/547 (0.73%) control 8/547 (1.46%)</p> <p>stillbirths DHA 2/547 (0.37%) control 3/547 (0.55%)</p> <p>total serious adverse events DHA 25/547 (4.57%) control 21/547 (3.84%)</p> <p>women reported nausea DHA 184/547 (33.7%) control 166/547 (30.3%)</p> <p>women reported vomiting DHA 147/547 (26.9%) control 130/547 (23.8%)</p>

Author, Year, Study	Intervention group and Adverse Event
Harper et al., 2010 ⁴³	<p>Intervention: Maternal</p> <p>admission to intensive/intermediate care nursery omega3 110/427 (25.9%) placebo 99/410 (24.6%)</p> <p>bronchopulmonary dysplasia omega3 9/425 (2.1%) placebo 6/403 (1.5%)</p> <p>interventricular hemorrhage, any grade omega3 10/427 (2.4%) placebo 9/410 (2.2%)</p> <p>interventricular hemorrhage, grade 3-4 omega3 5/427 (1.2%) placebo 3/410 (0.7%)</p> <p>necrotizing enterocolitis omega3 3/427 (0.7%) placebo 4/410 (1%)</p> <p>patent ductus arteriosus omega3 11/427 (2.6%) placebo 7/410 (1.7%)</p> <p>pregnancy loss or neonatal death omega3 16/434 (3.7%) placebo 17/418 (4.1%)</p> <p>proven sepsis omega3 5/427 (1.2%) placebo 3/410 (0.7%)</p> <p>received surfactant omega3 38/425 (8.9%) placebo 29/403 (7.2%)</p> <p>respiratory distress syndrome omega3 59/425 (13.9%) placebo 35/403 (8.7%)</p> <p>retinopathy of prematurity omega3 5/427 (1.2%) placebo 4/410 (1%)</p> <p>transient tachypnea omega3 31/425 (7.3%) placebo 24/403 (6%)</p>
Furuhjelm et al., 2009 ¹⁴⁹	<p>Intervention: Maternal and infant</p> <p>infant born with an atrioventricular defect and a coarctation of the aorta and needed surgery Intervention 1/52 (1.92%) control 0/65 (.)</p>
Fang et al., 2005 ¹²⁶	<p>Intervention: Preterm infants</p> <p>serious AE Neoangelac 0/11 (0%) Neoangelac Plus 0/16 (0%)</p>

Author, Year, Study	Intervention group and Adverse Event
Clandinin et al., 2005 ¹⁰⁴	<p>Intervention: Preterm infants</p> <p>adverse events for nervous system control 19/119 (16%) fish-DHA 8/130 (6%)</p> <p>bronchopulmonary dysplasia algal-DHA 16/112 (15%) control 17/119 (15%) fish-DHA 21/130 (17%)</p> <p>confirmed sepsis algal-DHA 19/112 (17%) control 16/119 (13%) fish-DHA 19/130 (15%)</p> <p>death during intial hospitalization control 2/119 (1.68%) fish-DHA 3/130 (2.31%)</p> <p>interventricular hemorrhage algal-DHA 14/112 (13%) control 32/119 (29%) fish-DHA 33/130 (27%)</p> <p>necrotizing enterocolitis algal-DHA 6/112 (5%) control 3/119 (3%) fish-DHA 7/130 (5%)</p> <p>retinopathy of prematurity algal-DHA 35/112 (47%) control 31/119 (42%) fish-DHA 53/130 (58%)</p>

Author, Year, Study	Intervention group and Adverse Event
<p>Henriksen et al., 2008¹⁰³</p> <p>Name of study: Unnamed Trial D</p>	<p>Intervention: Preterm infants</p> <p>NEC, treated, proven control 0/73 (0%) intervention 1/68 (1.5%)</p> <p>NEC, treated, suspected control 0/73 (0%) intervention 1/68 (1.5%)</p> <p>died before discharge control 2/73 (3%) intervention 0/68 (0%)</p> <p>intracranial hemorrhage, grade 1 control 7/73 (10%) intervention 6/68 (9%)</p> <p>intracranial hemorrhage, grade 2 control 5/73 (7%) intervention 3/68 (5%)</p> <p>intracranial hemorrhage, grade 3-4 control 1/73 (1.5%) intervention 2/68 (3%)</p> <p>need for respiratory support control 29/73 (40%) intervention 31/68 (46%)</p> <p>periventricular leukomalacia, 1 or 2 cysts on 1 side control 0/73 (0%) intervention 3/68 (4.5%)</p> <p>periventricular leukomalacia, >2 cysts or bilateral control 1/73 (1.5%) intervention 1/68 (1.5%)</p> <p>retinopathy, any retinopathy control 13/73 (18%) intervention 8/68 (12%)</p> <p>retinopathy, treated retinopathy control 3/73 (4%) intervention 3/68 (4%)</p>

Author, Year, Study	Intervention group and Adverse Event
<p>Makrides et al., 2009¹¹³</p> <p>Name of study: DINO</p>	<p>Intervention: Preterm infants</p> <p>Death high DHA 9/322 (8.89%) standard DHA 9/335 (2.8%)</p> <p>blindness high DHA 0/322 (5.07%) standard DHA 1/335 (0%)</p> <p>hearing loss high DHA 0/322 (0.3%) standard DHA 1/335 (0%)</p> <p>interventricular hemmorrhage high DHA 45/322 (2.09%) standard DHA 44/335 (13.98%)</p> <p>necrotizing enterocolitis high DHA 14/322 (2.69%) standard DHA 7/335 (4.35%)</p> <p>need for oxygen treatment high DHA 60/322 (0.3%) standard DHA 84/335 (18.63%)</p> <p>retinopathy of prematurity high DHA 74/322 (13.13%) standard DHA 73/335 (22.98%)</p> <p>seizures high DHA 7/322 (21.79%) standard DHA 17/335 (2.17%)</p>

Author, Year, Study	Intervention group and Adverse Event
Hoffman et al., 2008 ¹¹⁰	<p>Intervention: Term infants</p> <p>diarrhea DHA+ARA 5/96 (5.21%) control 8/86 (9.3%)</p> <p>fussiness DHA+ARA 6/96 (6.25%) control 6/86 (6.98%)</p> <p>gastroesophageal reflux DHA+ARA 3/96 (3.13%) control 13/86 (15.12%)</p> <p>poor weight gain DHA+ARA 0/96 (0%) control 2/86 (2.33%)</p> <p>serious AE unrelated to intervention DHA+ARA 6/96 (6.25%) control 6/86 (6.98%)</p> <p>type 1 glutaric acidemia DHA+ARA 0/96 (0%) control 1/86 (1.16%)</p> <p>vomiting DHA+ARA 4/96 (4.17%) control 8/86 (9.3%)</p> <p>weight loss DHA+ARA 0/96 (0%) control 3/86 (3.49%)</p>
Birch et al., 2005 ¹⁰⁷	<p>Intervention: Term infants</p> <p>withdrawal due to gastrointestinal intolerance LCP 17 wk 0/46 (0%) LCP 39 wk 1/44 (2.27%) LCP 52 wk 0/42 (0%) LCP 6 wk 4/47 (8.51%) control 17 wk 2/46 (4.35%) control 39 wk 0/46 (0%) control 52 wk 0/44 (0%) control 6 wk 3/48 (6.25%)</p> <p>withdrawal due to infant illness unrelated to formula LCP 17 wk 1/46 (2.17%) LCP 39 wk 1/44 (2.27%) LCP 52 wk 0/42 (0%) LCP 6 wk 0/47 (0%) control 17 wk 0/46 (0%) control 39 wk 0/46 (0%) control 52 wk 1/44 (2.27%) control 6 wk 0/48 (0%)</p>

Discussion

Overall Summary of Key Findings

For this systematic review, we identified 74 RCTs (in 75 publications) and 43 eligible prospective longitudinal studies and nested case-control studies that were eligible for inclusion based on the prespecified inclusion criteria. Most of the RCTs evaluated the effects of marine oil supplements on prenatal weight gain (risk for low birthweight) and length of gestation (risk for preterm birth) or the effects of DHA with or without AA as supplements or added to infant formulas on infant neural and cognitive development. Most observational studies assessed the association between the status of particular n-3 FA and developmental outcomes.

Within each category of analysis (by outcome, target of intervention, n-3 FA, and study design), studies diverged greatly with respect to the sources, doses, and durations of interventions; definitions or tests used to measure outcomes; and followup times. For outcomes such as visual, neurological, and cognitive development, by necessity, the tests used over time (in studies with multiple followups) changed to match maturity level. As a result, it was challenging to identify groups of studies that were sufficiently similar to pool, even with studies from the original report. In addition, many RCTs employed and reported the results of numerous outcome measures, which were often internally inconsistent or showed no apparent pattern over time. The majority of studies did not find statistically significant findings. Only a small number of observational studies that were excluded from the original report met the inclusion criteria for the current report, and the observational studies identified for the current report seldom assessed outcomes that were similar to those assessed in RCTs. Additional challenges are described in the Limitations section below.

The original report found inconsistent effects of prenatal maternal supplementation with DHA on length of gestation or the risk for preterm birth and a consistent finding of no effects of prenatal maternal supplementation with EPA+DHA among a large number of RCTs. The current report found similar findings for these outcomes in RCTs.

For the current report, pooled analysis of 10 RCTs among healthy pregnant women found a significant increase in length of gestations among mothers who received algal DHA or DHA-enriched fish oil (WMD +0.36 [95% CI 0.01, 0.71] weeks) compared to placebo. Pooled analysis of 6 RCTs showed no significant effect of DHA or DHA-enriched fish oil on the incidence of preterm birth.

Pooled analysis of 5 RCTs showed that maternal fish oil supplementation (EPA+DHA) had no significant effects on gestational age. Pooled analysis of 9 RCTs (in four publications) found no effects of EPA+DHA supplementation on the incidence of preterm birth. Prospective studies are sparse and found no consistent associations of maternal exposures with outcomes related to length of gestation or preterm birth.

The original report did not find a significant effect of maternal n-3 FA supplementation on the risk for low birth weight or SGA or a clear association of any maternal biomarkers with risk for low birth weight or birth weight itself. For the current report, we found a moderate level of evidence that maternal supplementation with DHA may increase birth weight, and a low level of evidence that maternal supplementation with EPA+DHA may not have significant effects on birth weight. Pooled analysis of 11 RCTs showed significantly higher birth weights among infants (mixed term and preterm) whose mothers received algal DHA or DHA-enriched fish oil compared with placebo (WMD [95% CI]=103.13 [6.83 199.43] grams). Pooled analysis of five RCTs found no effect of maternal EPA+DHA supplementation on infant birth weight. One RCT assessing the effects of ALA on infant birth weight showed no effects. These findings are consistent with

prospective studies, which found that higher maternal blood DHA concentrations were associated with higher birth weight.

There is also a low level of evidence that maternal supplementation with EPA+DHA may not have significant effects on risk for delivering a low birth weight infant among at-risk pregnant women, but the evidence is insufficient for the effects of maternal supplementation with DHA on risk for delivering a low birth weight infant among healthy pregnant women. Pooled analysis of four RCTs showed no significant effects of DHA+EPA supplementation (doses ranged from 2.0 to 3 g/d) on the incidence of small for gestational age between DHA+EPA supplementation and control groups (OR [95% CI]=1.00, CI[0.70, 1.43]). Pooled analysis of three RCTs identified for the current study that assessed the effects of DHA alone or DHA-enriched fish oil showed no significant effects on the risk for delivering a low birth weight infant among women who were not at risk. Observational studies were sparse and showed mostly no associations between n-3 intake or biomarkers and these outcomes.

The outcome of risk for antenatal and postnatal depression was a new one for this review. Three RCTs that assessed the effects of prenatal supplementation with DHA alone, DHA+AA, or EPA-enriched fish oil or postnatal supplementation with DHA alone found no effects on risk for developing perinatal depression among healthy pregnant women. Prospective studies found inconsistent associations of maternal n3FA levels and risk of developing perinatal depression.

The original report found no consistent effect of maternal supplementation with n-3FA on the risk for gestational hypertension or preeclampsia. Pooling one study identified for the current report and two studies from the original report that randomized high-risk women to DHA supplements or placebo resulted in a non-significant decrease in the risk for gestational hypertension or preeclampsia (OR 0.94[0.66, 1.34], $I^2=0\%$ (n=2,818); pooling studies of women not at high risk who were randomized to fish oil or placebo also showed no effect (OR 1.04 [0.76, 1.42], $I^2=0\%$).

The original report found no, or inconsistent, effects of maternal supplementation or infant formula fortification on postnatal growth patterns. For the current report, pooled analysis of five RCTs of prenatal supplementation with DHA and EPA or fish oil showed no significant effects on weight, length, or head circumference at 18 months. Pooled analysis of three studies of fortification of infant formula with DHA and AA also showed no effects on postnatal weight and length at 4 months among preterm infants.

The original report found no consistent effect of maternal or infant supplementation with n-3 FA on neurological developmental outcomes and inconsistent associations with biomarkers. Likewise, RCTs identified for the current report found no consistent effects of n-3 FA alone or in combination with n-6 FA on any of these outcomes compared with placebo. Two studies reported a positive effect of formula supplemented with DHA and AA on Bayley's PDI scores (an index of motor development) in preterm infants at 12 and 18 months, and two RCTs reported positive effects on brainstem maturation but mixed effects on gross motor control in term infants supplemented with DHA and similarly mixed effects of DHA plus AA.

The original report found inconsistent effects of maternal and infant supplementation with n-3 FA on visual acuity development and inconsistencies between behavioral measures and electrophysiological measures (VEP). The current report identified one RCT that found that DHA supplementation of breast-feeding mothers resulted in improvement in one VEP outcome at 4 and 8 months of age but not at 5 years of age. Another RCT reported that supplementing preterm infants with a high DHA:EPA fish oil did not influence visual acuity at 2 or 4 months. Pooling one new RCT and five RCTs from the original report show no significant effect of DHA plus AA

on infant visual acuity at 4 months but pooling one new study with three studies from the original report found a significant effect of DHA plus AA on visual acuity at 12 months. In full-term infants, one new RCT and two RCTs from the original report suggest a possible long-term effect of DHA supplementation but the outcome measures are inconsistent. Feeding full-term infants with a DHA plus AA-fortified supplement also showed signs of a beneficial effect on visual acuity maturation in three new studies, eight studies from the original report and a recent MA that included studies from both the current and original report.

The original report also found inconsistent effects of n-3 FA supplementation on cognitive development. Eight studies identified for the current report on supplementation of pregnant women (including one followup from the original report) showed no significant effects on cognitive outcomes in infants or children. Six RCTs identified for the current report on supplementation of breastfeeding women showed no significant effects on any cognitive outcomes. Six RCTs identified for the current report showed inconsistent effects of n-3 FA fortified supplement on cognitive developmental outcomes among infants born preterm. Four RCTs identified for the current report found inconsistent effects of n-3 FA fortification of supplement on cognitive outcomes: one study reported higher MDI scores at 18 months among toddlers who had received fortified formula. Among six observational studies identified for the current report, almost no associations were noted: In one study that controlled for 18 potential confounders, low levels of AA were associated with lower performance IQ and high levels of adrenic acid were associated with lower verbal IQ at age 8; low levels of DHA were associated with lower verbal and full scale IQ, however, the authors caution that the effect sizes were small. Because of heterogeneity, no studies identified for the current report could be pooled with each other or with studies from the original report.

Developmental outcomes newly included for the current report were the risk for Autism Spectrum Disorders (ASD), Learning Disorders, and Attention Deficit Hyperactivity Disorder (ADHD). Only one study was identified that assessed the association between n-3 FA and the risk for ASD; this study found no association. No studies were identified that explicitly assessed the association between n-3 FA intakes or exposures and the risk for learning disorders or ADHD.

Additional outcomes newly included in the current report were risks for atopic dermatitis/eczema, risks for allergies, and risks for respiratory illnesses, including asthma. A number of studies were conducted in mothers or infants at high familial risk for allergies or asthma. Four prenatal and three postnatal n-3 FA supplementation studies showed no significant effects on the risk for atopic dermatitis/eczema. Six of seven prospective observational studies also found no associations between n-3 FA exposures and risk for atopic dermatitis/eczema; however studies that assessed the association of biomarkers with this risk inconsistent associations with higher plasma levels of DHA, erythrocyte EPA, AA levels, and EPA/AA ratios. Metaanalysis of three RCTs that assessed the effect of maternal supplementation with DHA plus EPA showed a nonsignificant reduction in the risk for food allergies. Use of fortified infant formula did not influence the risk for allergies. Prospective observational studies showed no consistent associations of maternal or infant n-3 FA exposures with risk for allergies. Among seven RCTs that assessed the effect of prenatal n-3 FA supplementation on the risk for respiratory illnesses, only two reported significant effects, decreases in the risk for asthma, but these effects were not consistent over time. A metaanalysis of three postnatal interventions that assessed the effects of fortified formula on risk for wheeze found no significant effect. Prospective observational studies and biomarker studies reported inverse associations between various postnatal n-3 FA and n-6 FA exposures and risk for respiratory illnesses.

The original report identified 21 RCTs that reported on adverse events with n-3 FA supplementation in pregnant women, breastfeeding mothers, and preterm and term infants. Overall they found that n-3 FA supplements and fortified formulas were well tolerated. Pregnant and breastfeeding women reported no serious adverse events, and adverse events in these groups were limited to mild GI symptoms. Among both preterm and term infants, adverse events were largely limited to GI symptoms also, with most serious adverse events attributable to morbidities associated with prematurity. The current report identified 18 RCTs that reported on adverse events. The profile of both non-serious and serious adverse events in this report was identical to that of the original report. None of the observational studies identified for the current report described adverse events.

Too few studies assessed the effects of increasing doses of n-3 FA using similar populations and outcome measures to enable dose-response or threshold estimation.

Few studies stratified outcomes according to risk groups, so it was usually not possible to assess whether the effectiveness of omega-3 interventions depended on level of risk. In addition, no studies stratified outcomes by baseline n-3 FA status, so it is not possible to assess whether adequacy of n-3 FA status might account for differences in outcomes across (or lack of outcomes within) studies.

Limitations

Overall, both RCTs and observational studies included in this review had numerous quality concerns that could increase the risk for bias. Across RCTs, the most common risk-of-bias limitation was a lack of intention-to-treat analyses (47 percent of the included RCTs). Of included RCTs, 35 percent failed to describe allocation concealment sufficiently to determine whether it was adequate (and many studies failed to describe recruitment methods). Blinding of study participants contributed only slightly to potential risk of bias because participants were usually infants or children and outcomes were usually clinically apparent or assessed in a clinical laboratory. Twenty-seven percent of RCTs were at risk of attrition bias due to overall dropout rates greater than 20 percent, although most studies reported similar dropout rates between groups. Although 87 percent of the included RCTs reported similar baseline demographic characteristics between groups, 51 percent did not report baseline n-3 FA intake or status. This omission is a critical concern because baseline n-3 FA status likely affects response to changes in n-3 FA intake.

Across observational studies, the most common risk of bias limitation was the lack of representativeness of the cohorts to the population of interest: 37 percent were judged to be select populations or only somewhat representative. In most cases, these populations were described as having high intakes of fish; in several cases, the populations were at higher than average risk for the outcome of interest or another condition. Another reporting inadequacy related to the ranges and distribution of n-3 FA exposures. Of included observational studies, most of the n-3 FA dietary intake assessments included only dietary sources (not n-3 FA supplements). This issue does not affect the quality of biomarker data; however, so many different n-3 FA biomarkers were investigated across studies, that it was impossible to make comparisons.

Few studies reported adverse events, but among the 18 studies that did report adverse events, 55 percent did not predefine or prespecify adverse events to be queried, and none used a recognized categorization system to prespecify or sort categories or levels of intensity of adverse events reported. Only 30 percent reported an active mode of collection of adverse event information, and of the studies that reported serious adverse events (or lack thereof), most did not define “serious adverse event.” Of additional concern, studies of preterm infants often comingled

morbidities associated with prematurity (such as bronchopulmonary dysplasia and retinopathy of prematurity) and adverse events that might be associated with the intervention. Only one study that met inclusion criteria considered whether mercury exposure could account for the findings on the effects of fish oil intake, but the findings were equivocal.

Understandably, a number of the RCTs were conducted in women at risk for premature birth, gestational hypertension, a low birth weight infant, or women with a personal or family history of allergy or asthma. However, most observational studies examining the associations between dietary n-3 FA intake or biomarkers of n-3 FA intake and birth, respiratory, allergy, or developmental outcomes were conducted in generally healthy populations. Most RCTs were also small in size, although most reported doing power calculations. Observational studies that enrolled fewer than 250 were excluded by design.

Study interventions tended to be highly heterogeneous. Studies that labeled themselves as studies of DHA alone often included some amount of EPA as well as n-6 FA. Fish oil studies did not always report the oil's concentration of n-3 and n-6 FA in addition to the one of interest. Few studies assessed the effects of EPA alone and only one study assessed the effects of ALA alone. Of most concern was the heterogeneity in the description of the n-3 and n-6 FA contents of infant formulas and the systematic lack of assessment of formula intake (realizing the difficulty of this measurement in human infants). Few trials compared n-3 FA dose, formulation (e.g., ratio of EPA to DHA), or source. No trial compared different n-3 to n-6 FA ratios of supplements or intake. None of the observational studies attempted to determine a threshold effect of any associations between n-3 FA and the outcome of interest. Some observational studies failed to report median or range data of n-3 FA levels within quantiles, confidence intervals (or equivalent) of association hazard ratios, or conducted only linear analyses across a full range of n-3 FA values. In addition, studies varied in the range of n-3 FA status (e.g., intake level) within each study. The applicability of many of the observational studies to the U.S. population may also be limited by the higher baseline intakes of fish and other n-3 FA-containing foods and supplements among the populations in these studies.

For the outcomes related to infant and child development (except for growth patterns), tests used to measure most outcomes were numerous and heterogeneous across studies regardless of the study designs, and follow-up times varied widely. As a result, studies for a number of outcomes of interest could not be pooled, either with studies identified for the original report or with newly identified studies. In addition, the multiplicity of measures all but ensured that some outcome measure would produce a significant effect. Understandably, studies of cognitive, neurological, and visual acuity development with multiple follow-up points were required to use age/stage-appropriate outcome measures, but they seldom attempted to account for these changes in outcome measures.

The RCTs and observational studies differed in a number of ways, making it difficult to compare outcomes across the two study designs. Of note, the doses of n-3 FA supplements in RCTs were often much higher than the highest intake reported for observational studies. Furthermore, not all observational studies explicitly included n-3 FA supplements in their assessment of intake, and almost none of the RCTs attempted to account for background fish or n-3 FA intake as an effect modifier.

Finally, due to the significant heterogeneity across studies, the interpretation of overall meta-analysis results is limited. Only a small number of RCTs conducted dose response assessments (usually with poor results). For those reasons, we did not attempt to do dose-response meta-analysis of observational studies.

Future Research Recommendations

Future RCTs should be designed to determine whether particular populations or individuals are more likely to benefit from n-3 FA supplements or fortified formulas, e.g., individuals with relatively low baseline intakes of n-3 FA.

Therefore, studies need to measure—and match intervention groups according to—baseline n-3 FA biomarker status (although the current report has not clearly revealed the most relevant biomarkers). Researchers need to reach consensus on standardized formulations and on reporting of concentrations for interventions. The results of this review should help guide these decisions.

Studies also need to ascertain whether n-3 FA are more effective in individuals at increased risk for particular conditions (such as low birth weight, preterm birth, gestational hypertension, or for infants, risk for delayed visual acuity development or atopy).

Finally, identifying the most promising and clinically relevant outcome measures will be important to expanding the strength of the evidence base for the effectiveness of supplemental n-3 FA for maternal and childhood outcomes. The findings of large cohort studies are still needed to assess the potential role of n-3 FA status in the risk for conditions such as autism spectrum disorder, learning disabilities, and ADHD; however, it may be necessary first to identify clear intermediate risk factors for these conditions, because the length of followup needed for diagnosis of the conditions themselves greatly increases the potential interference of other confounding factors.

Conclusions

Maternal Exposures

Strength of evidence (SoE) is low for a small positive effect of algal docosahexaenoic acid (DHA) or DHA-enriched fish oil on length of gestation compared with placebo; strength of evidence is low regarding an apparent lack of effect of DHA or DHA-rich fish oil on risk for preterm birth. Strength of evidence is insufficient to draw conclusions about effects or associations for other n-3 FA alone or in combination. Observational studies did not show consistent associations of n-3 FA exposures (intake measurements or biomarkers) with these outcomes.

SoE is also moderate for a positive effect of algal DHA or DHA-enriched fish oil on birth weight but strength of evidence is insufficient to draw conclusions for the effects of most n-3 FA interventions on low birth weight or small-for-gestational age (SGA) infants; maternal n-3 FA biomarkers were significantly associated with birth weight, and low SoE supports an association of low early pregnancy plasma EPA and risk for SGA.

A low SoE supports a lack of effect of DHA or DHA-rich fish oil on (or association of n-3 FA with) risk for gestational hypertension. SoE is insufficient to draw conclusions about the effects of other n-3 FA interventions, either pre- or postnatal.

A moderate SoE supports a lack of effect of DHA supplementation on the risk for gestational hypertension or preeclampsia among high-risk pregnant women. SoE is insufficient to draw conclusions regarding the effects of other interventions.

Infant and Child Exposures

A moderate SoE supports a lack of effect of prenatal maternal supplementation with fish oil or DHA plus EPA on postnatal growth patterns (attainment of weight, length, and head circumference); a low SoE supports a lack of effect of pre- and postpartum maternal

supplementation on these outcomes. SoE is insufficient to draw conclusions about the effects of other pre- or postnatal maternal interventions. A low SoE supports a lack of effect of DHA plus AA-fortified infant formulas on growth patterns of preterm or term infants. SoE is insufficient regarding effects of other n-3 FA or supplementation at other times on growth patterns.

A moderate SoE supports a lack of consistent effect of prenatal DHA on development of visual acuity in infants. SoE is insufficient to draw conclusions regarding the effects of other n-3 FA supplementation of pregnant or breastfeeding women, and fortification of formula on development of visual acuity in preterm or term infants; SoE is insufficient to draw conclusions regarding the association of any biomarkers or intake of n-3 FA with visual acuity development.

A low SoE supports inconsistent effects of prenatal DHA on any measure of neurological development; insufficient SoE supports conclusions regarding the effects of any other n-3 FA supplementation of pregnant or breastfeeding mothers, or supplementation of preterm or term infants on measures of neurological development or associations of prenatal n-3 FA biomarker status and n-3 FA intakes with infant neurological development.

A low SoE supports a lack of consistent effect of maternal DHA supplementation on any measure of cognitive development. A moderate SoE supports a lack of association of other prenatal n-3 FA interventions with any cognitive outcomes. Low SoE supports a lack of effect of supplementing breastfeeding women with DHA plus EPA; the SoE for other postnatal interventions is insufficient to draw conclusions.

SoE is insufficient to draw conclusions regarding an association of n-3 FA status with risk for autism spectrum disorders. No studies were identified on n-3 FA and risk for attention deficit hyperactivity disorder or learning disabilities.

A low SoE supports inconsistent effects of prenatal or postnatal n-3 FA supplementation on the risk for atopic dermatitis/eczema and allergies and associations of biomarkers and intakes with these outcomes. A moderate SoE supports a lack of effect of prenatal and postnatal infant n-3 FA supplementation on the risk for asthma and other respiratory illnesses. A low level of evidence supports inconsistent associations between n-3 FA exposures and risk for respiratory illnesses.

Adverse Events

A moderate SoE supports a lack of serious adverse events (AEs) among pregnant women and infants who consume supplemental n-3 FA or foods fortified with n-3 FA; a moderate SoE supports a lack of non-serious AEs, with the exception of an increased risk for mild gastrointestinal symptoms, among pregnant women and infants who consume supplemental n-3 FA.

Overall Conclusions

Most studies identified for this report examined the effects of marine oil (or other combinations of DHA and EPA) supplements on pregnant or breastfeeding women or the effects of infant formula fortified with DHA plus arachidonic acid. As with the original report, with the exception of small effects on birth weight and length of gestation, n-3 FA supplementation or fortification seems to have no consistent effects on peripartum maternal or infant health outcomes. Future RCTs need to assess standardized preparations of n-3 and n-6 FA, using a select group of clinically important outcomes, on populations with baseline n-3 FA intakes typical of those of most western populations.

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Abbreviations / Acronyms

<u>Abbreviation</u>	<u>Meaning</u>
ALA	A-linolenic acid
AA	Arachidonic Acid
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ASD	Autism Spectrum Disorder
BDI	Beck Depression Inventory
BMI	Body mass index
CI	Confidence Interval
DHA	Docosahexaenoic acid
DPA	Docosapentaenoic acid
EAR	Estimated Average Requirement
EEG	Electroencephalogram
EFA	Essential fatty acid
EPA	Eicosapentaenoic acid
EPC	Evidence-based Practice Center
EPDS	Edinburgh Pregnancy Depression Scale
GHTN	Gestational hypertension
HR	Hazard ratio
IUGR	Intrauterine growth retardation
KQ	Key question
LBW	Low birth weight
LCPUFA	Long-chain polyunsaturated fatty acid
MA	Meta-analysis
MDI	Mental Development Index
n-3 FA	Omega-3 fatty acid(s)
n-6 FA	Omega-6 fatty acid(s)
NOS	Newcastle-Ottawa Scale or Neurological Optimality Score
NR	Not reported
ODS	Office of Dietary Supplements
OR	Odds ratio
PDI	Psychomotor Development Index
PE	Preeclampsia or eclampsia
PPD	Post- or peripartum depression
PUFA	Polyunsaturated fatty acid
RCT	Randomized controlled trial
RoB	Risk of bias
RR	Risk ratio
SDA	Stearidonic acid
SGA	Small for gestational age
SR	Systematic review
TEP	Technical expert panel